EFSA ; Scientific Opinion on Flavouring Group Evaluation 91, Revision 1 (FGE.91Rev1): Consideration of simple aliphatic and aromatic sulphides and thiols evaluated by JECFA (53rd and 68th meetings) structurally related to aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in FGE.08Rev3 (2011)

EFSA Publication

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 91, Revision 1 (FGE.91Rev1):

Consideration of simple aliphatic and aromatic sulphides and thiols evaluated by JECFA (53rd and 68th meetings) structurally related to aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in FGE.08Rev3 (2011)[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

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ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. The present consideration concerns a group of 47 simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 53rd meeting in 1999 and the 68th meeting in 2007. The revision is made due to consideration of two additional substances compared to previous version. The substances were evaluated through a stepwise approach that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. The Panel agrees with the application of the Procedure as performed by the

1 On request from the Commission, Question No EFSA-Q-2011-01016 & EFSA-Q-2011-01017, adopted on 24 November 2011.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Groups on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Leon Brimer, Wilfried Bursch, Angelo Carere, Riccardo Crebelli, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Catherine Leclercq, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Gerrit Speijers, Harriet Wallin and EFSA´s staff member Kim Rygaard Nielsen for the support provided to this EFSA scientific output.

Suggested citation: EFSA ; Scientific Opinion on Flavouring Group Evaluation 91, Revision 1 (FGE.91Rev1): Consideration of simple aliphatic and aromatic sulphides and thiols evaluated by JECFA (53rd and 68th meetings) structurally related to aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in FGE.08Rev3 (2011). EFSA Journal 2011; 9(12):2459. [72 pp.]. doi:10.2903/j.efsa.2011.2459. Available online: www.efsa.europa.eu/efsajournal.htm

JECFA for 34 substances considered in this FGE and agrees with the JECFA conclusion, "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach. Contrary to the JECFA, the Panel concluded for three substances [FL-no: 12.077, 12.108 and 12.162], which has been cleared by the JECFA at step B5 (the MSDI < 1.5 μg person per day), that adequate NOAELs exist and accordingly concluded at step B4 no safety concern at the estimated level of intake. Furthermore, for the trisulphides [FL-no: 12.114 and 12.256], contrary to the JECFA, the Panel concluded that no adequate NOAEL exists and that additional toxicity data are required. For eight substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252, 12.259 and 12.272] the Panel decided, also contrary to the JECFA, that the Procedure could not be applied due to concern for genotoxicity. So, the Panel concluded that 37 substances do not give rise to safety concern at their levels of dietary intake, estimated on the basis of the MSDI approach. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been considered for the substances evaluated through the Procedure and for three substances, [FL-no: 12.274, 12.284 and 15.049], information on the composition of stereoisomeric mixture is lacking.

SUMMARY

The Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) was asked to give scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The revision is made due to consideration of two additional substances [FL-no: 12.077 and 12.162] compared to previous version. Therefore, this consideration deals with 47 simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group, which are in the Register and which were evaluated by the JECFA at its 53rd and 68th meetings.

The Panel concluded that all the 47 substances in the JECFA flavouring groups of simple aliphatic and aromatic sulphides and thiols are structurally related to the aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by the European Food Safety Authority (EFSA) in the Flavouring Group Evaluation 08, Revision 3 (FGE.08Rev3). The 47 JECFA evaluated substances are distributed into eight subgroups of structurally related substances. The sub-grouping is the same as used in FGE.08Rev3.

The Panel agrees with the JECFA approach for 34 substances. However, for 13 substances [FL-no: 12.038, 12.077, 12.085, 12.108, 12.114, 12.137, 12.138, 12.145, 12.162, 12.252 12.256, 12.259 and 12.272], the Panel did not agree with the way the application of the Procedure was applied by the JECFA for the following reasons:

Eight substances (seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] and one sulphonate [FL-no: 12.272]) are structurally related to substances in FGE.08Rev3 {[FL-no: 12.172, 12.174] (subgroup III, monothiols), [FL-no: 16.057] (subgroup VII, mono-, di-, tri- and polysulphides with thioacetal structure) and [FL-no: 12.159] (subgroup X, sulphoxides/sulphones and sulphonates)} for which the Panel had identified concerns with respect to genotoxicity. Consequently adequate genotoxicity data are needed before these substances can be evaluated through the Procedure.

For five substances [FL-no: 12.077, 12.108, 12.114, 12.162 and 12.256] the Panel did not agree with the application of the Procedure by the JECFA for the following reasons:

For the two trisulphides [FL-no: 12.114 and 12.256], contrary to the JECFA, the Panel concluded that no adequate NOAEL exists and that additional toxicity data are required.

Finally, the Panel did not agree with the application of the Procedure by the JECFA for the substances [FL-no: 12.077, 12.108 and 12.162], which has been cleared by the JECFA at step B5 (the MSDI < 1.5 μg person per day). However, the Panel considers that adequate NOAELs exist for these substances and accordingly concluded at step B4 "No safety concern at the estimated level of intake".

For the remaining 34 substances the Panel agrees with the JECFA conclusion "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

For 36 substances use levels have been provided by the Industry. The mTAMDI figures calculated for five of these substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural class. For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For the remaining 11 of the 47 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267, 12.272 and 17.036] use levels are needed to calculate the mTAMDI values in order to identify those flavouring substances that need more refined exposure assessment.

In order to determine whether the conclusion for the 39 JECFA evaluated substances, for which the Panel concluded that they could be evaluated through the Procedure, can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria and identity are available for 35 substances evaluated through the Procedure. Information on the composition of the stereoisomeric mixture is lacking for three substances [FL-no: 12.274, 12.284 and 15.049] and information on solubility in ethanol for [FL-no: 12.162] is missing.

Thus, for five substances [FL-no: 12.114, 12.256, 12.274, 12.284 and 15.049] evaluated through the Procedure, the Panel has reservations (additional toxicity data are requested, or information on the composition of stereoisomeric mixture).

For 34 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, 12.264, 12.265, 12.267, 12.273, 12.275, 12.276, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297 and 17.036] the Panel agrees with the JECFA conclusion "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

KEY WORDS

Sulfides, sulphides, thiols, JECFA 68th meeting, JECFA 53rd meeting, food safety, FGE.91.

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996a) lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2009/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a).

Commission Regulation (EC) No 1565/2000 lays down that substances that are contained in the Register and will be classified in the future by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) so as to present no safety concern at current levels of intake will be considered by the European Food Safety Authority (EFSA), who may then decide that no further evaluation is necessary.

In the period 2000 – 2008, during its 55th, 57th, 59th, 61st, 63rd, 65th, 68th and 69th meetings, the JECFA evaluated about 1000 substances, which are in the EU Register.

TERMS OF REFERENCE

EFSA is requested to consider the JECFA evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a). These flavouring substances are listed in the Register which was adopted by Commission Decision 1999/217 EC (EC, 1999a) and its consecutive amendments.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999a), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the "JECFA Procedure". The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be put through the EFSA Procedure.

The following issues are of special importance.

Intake

In its evaluation, the Panel as a default uses the "Maximised Survey-derived Daily Intake" (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe.

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available,

meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach. It is noted that the JECFA, at its 65th meeting considered "how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods" (JECFA, 2006c).

In the absence of more accurate information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a "modified Theoretical Added Maximum Daily Intake" (mTAMDI) approach based on the normal use levels reported by Industry.

As information on use levels for the flavouring substances has not been requested by the JECFA or has not otherwise been provided to the Panel, it is not possible to estimate the daily intakes using the mTAMDI approach for the substances evaluated by the JECFA. The Panel will need information on use levels in order to finalise the evaluation.

Threshold of 1.5 Microgram/Person/Day (Step B5) Used by the JECFA

The JECFA uses the threshold of concern of 1.5 microgram/person/day as part of the evaluation procedure:

"The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 microgram per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 microgram per day?") (JECFA, 1999b).

In line with the Opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 microgram per person per day.

Genotoxicity

As reflected in the Opinion of SCF (SCF, 1999a), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *in vitro,* will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of the JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

In the consideration of the JECFA evaluated substances, the Panel will examine the structural relationship and metabolism features of the substances within the flavouring group and compare this with the corresponding FGE.

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

The EFSA consideration in FGE.91 dealt with 45 substances, forty simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 68th meeting, 2007 and five tertiary thiols evaluated by JECFA at the 53rd meeting, 1999.

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.91	24 September 2009	http://www.efsa.europa.eu/en/efsajournal/pub/1337.htm	45
FGE.91Rev1	23 november 2011		47

The present revision of FGE.91, FGE.91Rev1, includes the assessment of two additional substances, benzyl methyl sulphide and methyl phenyl sulfide [FL-no: 12.077 and 12.162]. These substances have been evaluated by the JECFA at the 53rd meeting in 1999. The reason for the inclusion of these substances is explained in Section 1.1.2.

Furthermore, additional information has been submitted on stereoisomerism on [FL-no: 12.108, 12.264, 12.267, 12.273, 12.274, 12.284, 12.285, 12.286, 12.287, 12.289, 12.290, 12.292, 12.297 and 15.049], on specifications for [Fl no: 12.038, 12.253, 12.256, 12.274, 12.276, 12.284 and FL-no: 12.297] and on composition of mixture for [FL-no: 12.153, 12.254, 12.256, 12.259].

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. Status

The JECFA has evaluated a group of 51 flavouring substances consisting of simple aliphatic and aromatic sulphides and thiols at the 68th meeting (JECFA, 2008b).

The JECFA has at the 53rd meeting (JECFA, 2000c), before 2000, evaluated a group of 137 flavouring substances consisting of simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group.

1.1.2. EFSA Considerations

This FGE only deals with 47 of the above mentioned 188 substances: forty substances evaluated by the JECFA at the 68th meeting, 2007, and seven substances evaluated by JECFA at the 53rd meeting, 1999 because:

- Of the 51 simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 68th meeting six are not in the Register (methionyl butyrate (JECFA-no: 1668), S-Ethyl 2-acetylaminoethanethionate (JECFA-no: 1680), (±)-3-(Ethyl-thio)butanol (JECFA-no: 1703), (±)-3-mercapto-1-butyl acetate (JECFA-no: 1705), 3-mercapto-3-methyl-1-butyl acetate (JECFA-no: 1706), 2,5-dithiahexane (JECFA-no: 1707) and five substances have already been

evaluated in FGE.08 [FL-no: 12.120, 12.165, 12.191, 12.199 and 12.214]. The remaining 40 substances from the 68th meeting will be considered in the present FGE.

- Of the 137 simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated group evaluated by the JECFA at the 53rd meeting five are tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145] used as supporting substances in FGE.08 and following revisions. These substances were evaluated by the JECFA before the year 2000. For flavouring substances evaluated by the JECFA before 2000 it is laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a) that if they are considered acceptable, at the estimated levels of intake, by the JECFA and comply with the general use criteria, they could be included in the list of authorised substances without undergoing a separate evaluation for the time being. However, in FGE.08Rev1 the genotoxicity issues that were noted for candidate tertiary thiols are obviously also of relevance for the five supporting JECFA-evaluated tertiary thiols in FGE.08Rev1. Furthermore, two of the 137 substances are acyclic sulphides [FL-no: 12.077 and 12.162], which the JECFA evaluated at step B5; No NOAEL exists to provide a margin of safety, but as the estimated intake in the USA of 0.02 and 0.4 µg/*capita*/day, respectively, are below the threshold of concern of 1.5 µg/person/day the JECFA Committee would not expect the two substances to present a safety concern when used as flavouring substances. However, in line with the Opinion expressed by the Scientific Committee on Food (SCF, 1999a), the Panel does not make use of this threshold of 1.5 µg/person/day. Accordingly, these seven substances (i.e. 5 tertiary thiols and two sulphides) from the 53rd meeting are also considered.

The Panel concluded that the substances in the JECFA flavouring groups of simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group are structurally related to the group of aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in the Flavouring Group Evaluation 08 (FGE.08) and following revisions .

The substances in FGE.08 and the following revisions were divided in subgroups. The 47 JECFA evaluated substances considered here, are assigned to the following eight subgroups: Acyclic sulphides (I), Monothiols (IIIa & IIIb), Dithiols (IV), Acyclic and cyclic disulphides (V), Acyclic polysulphides (VI), Mono, di-, tri- and polysulphides with thioacetal structure (VII), Thioesters (VIII) and Sulphoxides/sulphones and sulphonates (X). No substances in the current FGE are related to subgroup II, IX and XI from FGE.08 or the following revisions. The subgroups in the latest revision, FGE.08Rev3 are shown in Annex I.

1.2. Isomers

1.2.1. Status

The following 21 substances [FL-no: 12.038, 12.085, 12.108, 12.252, 12.259, 12.264, 12.267, 12.273, 12.274, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.297, 15.049 and 17.036] in the group of JECFA evaluated simple aliphatic and aromatic sulphides and thiols have a chiral centre. Furthermore one substance [FL-no: 12.265] can exist as geometrical isomers.

1.2.2. EFSA Considerations

The stereoisomeric composition has not been specified for four substances [FL-no: 12.038, 12.085, 12.252 and 12.259]. For three substances [FL-no: 12.274, 12.284 and 15.049], information on the composition of the stereoisomeric mixture is lacking. Industry has informed that the three substances occurs as a mixture of diastereoisomers (EFFA, 2010a), however, the composition of the mixture has to be specified (see Table 1).

1.3. Specifications

1.3.1. Status

The European Flavour Industry has submitted specifications for the substances commercially used in Europe (EFFA, 2004ak; EFFA, 2006u; EFFA, 2010a; EFFA, 2011k; Flavour Industry, 2004m; Flavour Industry, 2005h; Flavour Industry, 2006x; Flavour Industry, 2007i; Flavour Industry, 2007j). Although the JECFA specifications are available, the specifications used in this consideration are those submitted by the Industry for the 40 substances considered by the JECFA at the 68th meeting. For the remaining seven substances (from 53rd meeting) the JECFA specifications are used (JECFA, 1999c). See Table 1.

1.3.2. EFSA Considerations

Specifications including complete purity criteria and identity tests are available for 38 substances. For the remaining seven substances considered in the present FGE the following information is lacking: Stereoisomeric composition for substances [FL-no: 12.038, 12.085, 12.252 and 12.259], composition of stereoisomeric mixture for [FL-no: 12.274, 12.284 and 15.049], refractive index and specific gravity for [FL-no: 12.145] and solubility in ethanol for [FL-no: 12.085 and 12.162].

2. Intake Estimations

2.1. Status

For 43 substances evaluated through the JECFA Procedure intake data are available for EU (JECFA, 2008b; EFFA, 2011d). For the remaining three substances [FL-no: 12.137, 12.138 and 12.145] production figures are only available for the USA (see Table 3.1).

2.2. EFSA Considerations

Of the in total 47 substances evaluated through the JECFA Procedure, 41 substances have intake data for the EU available from the JECFA evaluation (JECFA, 2008b; EFFA, 2011d) and for three substances [FL-no: 12.256, 12.284 and 17.036] the Industry has submitted production figures for EU to EFSA. These data have been used in the present consideration (see Table 2.2.2 and 3.1).

As production figures are available only for the USA for [FL-no: 12.137, 12.138 and 12.145] MSDI values for the EU cannot be calculated for these three substances.

For 36 of the 47 substances normal and maximum use levels have been provided by the Flavour Industry (EFFA, 2004ak; EFFA, 2006u; Flavour Industry, 2004m; Flavour Industry, 2005h; Flavour Industry, 2006x; Flavour Industry, 2007i) in accordance with the Commission Regulation (EC) No 1565/2000 (EC, 2000a) (see Annex I, Table 2.2.1). Based on these normal use levels, mTAMDI figures (see Annex I, Table 2.2.2) can be calculated (for calculation of mTAMDI figures, see e.g. FGE.08Rev3, Annex II (EFSA, 2010w).

The mTAMDI figures calculated for five substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural classes (see Annex I, Table). For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For 11 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267, 12.272 and 17.036] for which use levels have not been provided, use levels are needed to calculate the mTAMDI values in order to identify those flavouring substances that need more refined exposure assessment.

3. Genotoxicity Data

3.1. Genotoxicity Studies - Text Taken[4] from the JECFA (JECFA, 2008b)

In vitro

No evidence of mutagenicity was observed when allylthio hexanoate [FL-no: 12.275], 3,6-diethyl-1,2,4,5-tetrathiane [FL-no: 12.274] or allyl propyl disulfide [FL-no: 12.021] were incubated with *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535 and/or TA1537 with and without metabolic activation at concentrations of up to 5000 µg/plate (Eder et al., 1980; Eder et al., 1982b; Zeiger et al., 1988; King and Harnasch, 2002a; Uhde, 2005).

No evidence of mutagenicity was observed when the structurally related substances tetrahydrothiophene [FL-no: 15.102], 2-methylpropane-2-thiol [FL-no: 12.174] and methyl methanethiosulfonate [FL-no: 12.159] were incubated with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and/or TA2637 with and without metabolic activation at concentrations of up to 10 000 µg/plate (Dorange et al., 1983; Pennwalt Corporation, 1987a-d; Phillips Petroleum Company, 1990a).

Tetrahydrothiophene [FL-no: 15.102] tested negative in a cytogenetic assay with human lymphocytes, a mutation assay at the HPRT chromosome with Chinese hamster ovary (CHO) cells and an unscheduled deoxyribonucleic acid (DNA) synthesis test with human epithelial cells performed with and without metabolic activation at concentrations of up to 5120 µg/ml (Pennwalt Corporation, 1987a-d).

In the absence of an exogenous metabolic activation system, an increase was observed in the induction of forward mutations when L5178Y*tk*(+/–) mouse lymphoma cells were exposed to 2-methylpropane-2-thiol [FL-no: 12.174] at the two highest tested concentrations (i.e. 202 and 1000 µg/ml); however, in the presence of such a system, 2-methylpropane-2-thiol yielded negative results at concentrations of up to 1000 µg/ml (Phillips Petroleum Company, 1990a). Mouse lymphoma assays conducted in the absence of metabolic activation for simple aliphatic and aromatic substances have been shown to be inconsistent with the results of other standardized genotoxicity assays. Moreover, culture conditions of low pH and high osmolality have been shown to produce false-positive results in *in vitro* genotoxicity assays (Cifone et al., 1987; Galloway et al., 1987a; Heck et al., 1989). Therefore, it is not unexpected that other low molecular weight thiols (e.g. ethanethiol [FL-no: 12.017] and butane-1-thiol [FL-no: 12.010]) have been shown to produce equivocal or positive evidence of mutagenicity in the mouse lymphoma forward mutation assay, while being negative in reverse mutation assays (Eder et al., 1980; Eder et al., 1982b; Zeiger et al., 1988; King and Harnasch, 2002a; Uhde, 2005). Furthermore, dibutyl disulphide [FL-no: 12.111] yielded negative results in a mouse lymphoma forward mutation assay without metabolic activation; however, the concentrations tested in this trial were not specified (Dooley et al., 1987).

Tetrahydrothiophene [FL-no: 15.102] and 2-methylpropane-2-thiol [FL-no: 12.174] were negative in a sister chromatid exchange (SCE) assay with CHO cells at concentrations of up to 125 and 1350 µg/ml, respectively, with and without metabolic activation (Pennwalt Corporation a-d; Phillips Petroleum Company, 1990). Although a statistically significant increase in the number of SCEs was observed at concentrations of 450 and 1350 µg 2-methylpropane-2-thiol/ml, there was a lack of significant increases at lower test concentrations. Additionally, although statistically significant, the increases in SCEs were less than 2-fold greater than in controls. As such, the authors concluded 2-methylpropane-2-thiol to be non-mutagenic (Phillips Petroleum Company, 1990a).

[4] *The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed*.

Methyl methanethiosulfonate [FL-no: 12.159] was negative in chromosomal aberration assays conducted in *Saccharomyces cerevisiae* strain D7 or *S. cerevisiae* haploid strain N123 at concentrations of up to 300 µg/ml (Dorange et al., 1983).

Conclusion on genotoxicity

The testing of these representative materials *in vitro* in prokaryotic and eukaryotic test systems indicates that this group of simple aliphatic and aromatic sulphides and thiols is not expected to exhibit any mutagenic or genotoxic properties.

For a summary of *in vitro / in vivo* genotoxicity data considered by the JECFA see Table 2.1.

3.2. Genotoxicity Studies - Text Taken[5] from EFSA FGE.08Rev3 (EFSA, 2010w)

Only text from the relevant subgroups (subgroup I, III, IV, V, VI, VII, VIII and X) are shown here (See Annex I for definition of the subgroups).

In vitro / in vivo

Genotoxicity *in vitro* data are available for four candidate substances: di-(1-propenyl)-sulfid (mixture) [FL-no: 12.298] (subgroup I); 2-methylpropane-2-thiol [FL-no: 12.174] (subgroup III); dibutyl disulfide [FL-no: 12.111] (subgroup V), and methyl methanethiosulfonate [FL-no: 12.159] (subgroup X). In addition studies are available on 13 supporting substances from subgroups I (1), III (4), IV (1), V (4), VIII (2) and X (1).

In vivo data are available for one candidate substance [FL-no: 12.159] (subgroup X) and for four supporting substances from subgroups I (1), III (1), V (1) and VI (1).

Subgroup I (Acyclic sulphides)

In vitro data are available for the candidate substance, di-(1-propenyl)-sulfide [FL-no: 12.298]; Ames test: *S. typhimurium* TA98, TA100, TA102, TA1535, TA1537, 1-100 microg/plate. Result was negative with and without metabolic activation (Stien, 2005c).

For supporting substances, only data on diallyl sulfide [FL-no: 12.088] are available: diallyl sulfide was negative in a limited bacterial reversion assay using one strain only (TA100) and provided equivocal results in an *in vitro* cytogenetic test in which increased incidences of cells with chromosomal aberrations and sister chromatid exchanges (SCEs), statistically significant but not dose related, were observed. *In vivo* diallyl sulfide was evaluated as negative in a micronucleus test in mouse bone marrow, which was, however, not designed to evaluate the genotoxicity of the substance itself as it was tested in a mixture. Overall the data available do not allow evaluation of the genotoxicity of the substances of this subgroup.

Subgroup III (Monothiols)

2-Methylpropane-2-thiol [FL-no: 12.174] is reported to be negative in an Ames test. It is reported to be positive in a mouse lymphoma assay without metabolic activation and negative in the test with metabolic activation, and it is reported to be negative in an *in vitro* SCE assay. However, these studies are reported only as summaries (Phillips Petroleum Company, 1990a). Some details are available for methods but not for the results. Although the validity of these studies cannot be fully evaluated, the positive result in the mouse lymphoma assay raises concern with respect to the potential for genotoxicity of this tertiary thiol and structurally related compounds, i.e. 2-methylbutane-2-thiol [FL-no: 12.172] and the five supporting substances [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145].

[5] *The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed*.

The *in vitro* data available for the other substances in this subgroup do not provide indication of concern for genotoxicity.

Subgroup IV (Dithiols)

Equivocal results were reported for the only supporting substance tested. 1,2-Ethanedithiol [FL-no: 12.066] was evaluated positive for induction of gene mutations and SCEs *in vitro* in a poorly reported study. However, increased mutation frequencies were associated with unacceptably high toxicity, and the relevance of SCEs for genotoxicity assessment is unclear. Moreover, the validity of the latter data set is questionable, as the distinct effect of S9 on toxicity observed in the other mammalian cell mutation study was not replicated. 1,2-Ethanedithiol [FL-no: 12.066] was reported in an abstract to be negative in the Ames test.

Subgroup V (Acyclic and Cyclic dipolysulphides)

Dibutyl disulfide [FL-no: 12.111] is reported to be negative in a mouse lymphoma assay (Dooley et al., 1987). However, the study is reported only as abstract, and thus, the validity cannot be evaluated.

Further data are available for the supporting substances diallyl disulfide [FL-no: 12.008], dimethyldisulfide [FL-no: 12.026], phenyl disulfide [FL-no: 12.043] and benzyl disulfide [FL-no: 12.081]. All substances were negative in the Ames test. In addition, diallyl disulfide was reported to be positive in a chromosomal aberration assay *in vitro*, with and without metabolic activation, and weakly positive in a SCE assay. However, the validity of these findings is doubtful as chromosomal aberrations were only increased in conditions associated with extensive (> 90 %) lethality, and because of the limitation of SCE in genotoxic hazard identification.

Subgroup VII (Mono-, di-, tri- and polysulphides with thioacetal structure)

There are no data available on genotoxicity for the substances in this group. However, one of the hydrolysis products of the candidate substance 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057] is structurally related to the above-mentioned tertiary thiols, raising concern with respect to the genotoxicity of this candidate. Therefore, in the absence of further genotoxicity data, the Panel concluded that the Procedure could not be applied to 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057].

Subgroup VIII (Thioesters)

The *in vitro* data available on supporting substances provide no indication of concern for genotoxicity.

Subgroup X (Sulphoxides/sulphones and sulphonates)

Methyl methanethiosulfonate (MMTS) [FL-no: 12.159] is structurally similar to methyl methanesulfonate (MMS), a direct acting genotoxic carcinogen. However, the presence of an additional sulphur is expected to decrease the electrophilicity and therefore the possible genotoxicity of the candidate substance. MMTS is reported to be negative in an Ames test and in a mitotic recombination/mutagenicity assay with *Saccharomyces cerevisiae* (Dorange et al., 1983). However, as pointed out by the authors, thiosulphonates in general, and MMTS in particular, are non-specific antimicrobial agents that are active at low concentrations on bacteria, as well as on yeast and other fungi. Therefore, bacterial test systems and yeast assays are not appropriate to evaluate genotoxicity of thiosulphonates. MMTS [FL-no: 12.159] has also been shown to be negative in an assay performed with *Nicotiana tabacum* seeds (Dorange et al., 1983), but the relevance of this test is unknown.

Antimutagenic activity has been shown for MMTS, which occurs naturally in some vegetables from Cruciferae and Liliaceae species (Marks et al., 1993; Nakamura et al., 1993; Nakamura et al., 1996; Ito et al., 1997; Nakamura et al., 1997a). However, antimutagenicity studies *per se* are not specifically designed to evaluate the genotoxic potential of chemicals.

In conclusion, the limited relevance of the tests carried out so far in bacteria and yeasts and the lack of tests on mammalian cells do not allow an adequate evaluation of the genotoxic potential of MMTS. In addition, the similarity with MMS raises concern with respect to the genotoxicity of this candidate substance.

Methylsulfinyl methane [FL-no: 12.175] (synonym: dimethylsulphoxide, DMSO) was reported to be positive in an Ames test at high doses, which resulted in reduced bacterial survival. The validity of this finding is highly questionable compared to the overwhelming evidence on absence of genotoxic properties provided by the wide use of DMSO as solvent for test material in genotoxicity assays including controls for solvent activity. Further data on other supporting substances are of limited or insufficient quality and cannot be evaluated.

Conclusion on genotoxicity

Most *in vitro* and *in vivo* studies are of limited or insufficient quality and provide only limited information.

The available data raise concern with respect to genotoxicity of two tertiary thiols [FL-no: 12.172 and 12.174], included as candidate substances in subgroup III. Hydrolysis of the candidate substance 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057], included in subgroup VII, leads to the formation of a tertiary thiol structurally related to the above-mentioned compounds. Therefore, there is also concern with respect to genotoxicity of this candidate substance. The Panel noted that in FGE.08 five of the supporting substances were tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145] for which a concern for genotoxicity has been raised in the present FGE, FGE.08Rev3. These supporting substances have been evaluated by the JECFA at the 53rd meeting (JECFA, 2000b; JECFA, 2000c) and are not scheduled for evaluation by EFSA. However, these substances should be considered by Panel based on the outcome of the evaluation of the two candidate tertiary thiols [FL-no: 12.172 and 12.174].

In addition, genotoxicity of the candidate substance MMTS [FL-no: 12.159], included in subgroup X, could not be assessed from the data available. However, due to the similarity with MMS, a direct acting mutagen and carcinogen, there is concern with respect to genotoxic potential of this candidate substance.

Therefore, the Panel decided that the Procedure could not be applied to the four candidate substances [FL-no: 12.159, 12.172, 12.174 and 16.057] until adequate *in vivo* genotoxicity data become available.

The other *in vitro / in vivo* genotoxicity data available, often from limited or poorly reported studies, do not provide clear indication of concern for genotoxicity for the remaining candidate substances included in the present evaluation.

For a summary of *in vitro / in vivo* genotoxicity data considered by EFSA in FGE.08Rev3, see Table 2.2 and Table 2.3.

3.3. EFSA Considerations

The group of substances evaluated by the JECFA and evaluated in the present FGE.91Rev1 includes seven tertiary thiols, 8-mercapto-p-menthan-3-one, p-menth-1-ene-8-thiol, 3-mercapto-3-methylbutan-1-ol, 3-mercapto-3-methylbutyl formate, 4-methoxy-2-methylbutane-2-thiol, 4-mercapto-4-methyl-2-pentanol and 1-mercapto-p-menthan-3-one [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259]. These substances are structurally related to substances evaluated in FGE.08Rev3, the two tertiary thiols 2-methylbutane-2-thiol and 2-methylpropane-2-thiol [FL-no: 12.172 and 12.174], and the tertiary thiol resulting from hydrolysis of 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057] for which three substances the Panel identified concern with respect to genotoxicity, see Section 3.2.

The Panel further noted that the substance propyl propanethiosulphonate [FL-no: 12.272] in the present FGE.91Rev1 shows structural similarity to a substance evaluated in FGE.08Rev3, methyl methanethiosulphonate [FL-no: 12.159], for which there was concern with respect to genotoxicity due to structural similarities to the direct acting carcinogen methyl methanesulphonate.

For the remaining 39 substances in the present FGE.91Rev1 the Panel considered that the available data on genotoxicity do not preclude their evaluation through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to Simple Aliphatic and Aromatic Sulphides and Thiols by the JECFA (JECFA, 2000c; JECFA, 2008b)

Note: The JECFA evaluated substances not in the Register, are identified by their four digit JECFA number in the following text.

Step 1.

In applying the Procedure for the Safety Evaluation of Flavouring Agents to these 47 flavouring agents considered in this FGE, the Committee assigned 33 [FL-no: 12.012, 12.017, 12.114, 12.126, 12.130, 12.134, 12.137, 12.138, 12.145, 12.146, 12.153, 12.240, 12.242, 12.243, 12.252, 12.253, 12.254, 12.256, 12.264, 12.265, 12.267, 12.273, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12,290, 12.292, 12.293, 12.294 and 12.297] to structural class I and 10 [FL-no: 12.021, 12.038, 12.077, 12.085, 12.162, 12.259, 12.274, 12.275, 12.289 and 15.049] to structural class II. The remaining four flavouring agents [FL-no: 12.108, 12.139, 12.272, and 17.036] were assigned to structural class III (Cramer et al., 1978).

Step 2.

None of the flavouring agents in this group can be predicted to be metabolized to innocuous products. The evaluation of these substances therefore proceeded via the B-side of the Procedure.

Step B3.

The estimated daily per capita intakes of the 33 flavouring agents in this group in structural class I are below the threshold of concern (i.e. 1800 microg/person per day for class I). The estimated daily per capita intakes of the 10 flavouring agents in structural class II are below the threshold of concern (i.e. 540 microg/person per day for class II). The estimated daily per capita intakes of the four flavouring agents in structural class III are below the threshold of concern (i.e. 90 microg/person per day for class III). Accordingly, the evaluation of all the substances in the group proceeded to Step B4.

Step B4.

For 2-methyl-1-methylthio-2-butene [FL-no: 12.265], the no-observed effect level (NOEL) of 250 mg/kg body weight (bw) per day for the structurally related substance methyl sulfide [FL-no: 12.006] from a 98-day study in male and female rats (Butterworth et al., 1975b) provides an adequate margin of safety (at least 125 million) in relation to currently estimated levels of intake of this substance from its use as a flavouring substance. This NOEL is also appropriate for the structurally related substances 2,4,6-trithiaheptane [FL-no: 12.240] and 2,5-dithiahexane (No. 1707), because they are all simple sulfides that are anticipated to undergo oxidation and subsequent metabolism via similar metabolic pathways. In relation to the currently estimated levels of intake from use as flavouring substances, the

NOEL of 250 mg/kg bw per day provides adequate margins of safety of > 1 billion[6] and 125 million for 2,4,6-trithiaheptane [FL-no: 12.240] and 2,5-dithiahexane (No. 1707), respectively.

For methionyl butyrate (No. 1668), the NOEL of 1.4 mg/kg bw per day for the structurally related substance 2-(methylthiomethyl)-3-phenylpropenal [FL-no: 12.087] from a 92-day study in male rats (Cox et al., 1979) provides an adequate margin of safety (7 million) in relation to currently estimated levels of intake of this substance from its use as a flavouring substance. This NOEL is also appropriate for the structurally related substances (±)-isobutyl 3-methylthiobutyrate [FL-no: 12.214], methyl (methylthio)acetate [FL-no: 12.146] and (±)-3-(methylthio)heptanal [FL-no: 12.273], because they are all acyclic sulfides with oxidized sidechains. For these structurally related substances, the NOEL of 1.4 mg/ kg bw per day provides adequate margins of safety in the range of 28 000 to 7 million in relation to the currently estimated levels of intake from use as flavouring agents.

For methylthiomethylmercaptan [FL-no: 12.242], the NOEL of 0.3 mg/kg bw per day for the structurally related substance 3-methyl-1,2,4trithiane [FL-no: 15.036] from a 90-day study in rats (Mondino, 1981a) provides an adequate margin of safety (at least 150 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For 3-(methylthio)-2-butanone [FL-no: 12.285] and (±)-3-(ethylthio)butanol (No. 1703), the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2-mercapto-3-butanol [FL-no: 12.024] from a 90-day study in rats (Cox et al., 1974a) provides adequate margins of safety (> 3 million and 350 000, respectively) in relation to estimated levels of intake of these substances from their use as flavouring agents.

For 4-(methylthio)-2-pentanone [FL-no: 12.286], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3-mercapto-2-pentanone [FL-no: 12.031] from a 90-day study in rats (Morgareidge, 1971b) provides an adequate margin of safety (> 9 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For methyl 3-(methylthio)butanoate [FL-no: 12.287], the NOEL of 6.5 mg/ kg bw per day for the structurally related substance ethyl thioacetate [FL-no: 12.018] from a 91-day study in rats (Shellenberger, 1970b) provides an adequate margin of safety (> 32 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For *S*-allyl-L-cysteine [FL-no: 17.036], the NOEL of 250 mg/kg bw per day from a 28-day study in rats (Kodera et al., 2002) provides an adequate margin of safety (> 8 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For (±)-2,8-epithio-*cis*-*p*-menthane [FL-no: 12.120], the NOEL of 10 mg/kg bw per day in female rats from a 28-day study (Finlay, 2004) provides an adequate margin of safety (> 1 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethanethiol [FL-no: 12.017], the NOEL of 0.56 mg/kg bw per day for the structurally related substance cyclopentanethiol [FL-no: 12.029] from a 90-day study in male and female rats (Morgareidge and Oser, 1970b) provides an adequate margin of safety (at least 80 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances 1-pentanethiol [FL-no: 12.191], 1-heptanethiol [FL-no: 12.130] and 2-heptanethiol [FL-no: 12.288], because they are all simple thiols. For these structurally related substances, the NOEL of 0.56 mg/ kg bw per day provides adequate margins of safety in the range of > 100 000 to > 2 million in relation to the currently estimated levels of intake from use as flavouring agents.

[6] Note that billion is defined as a thousand million (10^9).

For (±)-1-phenylethylmercaptan [FL-no: 12.289], the NOEL of 0.43 mg/ kg bw per day for the structurally related substance 2,6-dimethylthiophenol [FL-no: 12.082] from a 90-day study in rats (Peano et al., 1981) provides an adequate margin of safety (> 2 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For propyl 2-mercaptopropionate [FL-no: 12.267], the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2-mercapto-3-butanol [FL-no: 12.024] from a 90-day study in rats (Cox et al., 1974a) provides an adequate margin of safety (at least 350 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances (±)-4-mercapto-4-methyl-2-pentanol [FL-no: 12.252], (*S*)-1-methoxy-3-heptanethiol [FL-no: 12.276], methyl 3-mercaptobutanoate [FL-no: 12.290]), hexyl 3-mercaptobutanoate [FL-no: 12.292], (±)-3-mercapto-1-butyl acetate (No. 1705), 3-mercapto-3-methyl-1-butyl acetate (No. 1706), 3-mercaptoheptyl acetate [FL-no: 12.297] and *cis*-and *trans*-mercapto-*p*-menthan-3-one [FL-no: 12.259], because they are all thiols with oxidized side-chains. For these structurally related substances, the NOEL of 0.7 mg/kg bw per day provides adequate margins of safety in the range of > 23 000 to > 3 million in relation to the currently estimated intakes from use as flavouring agents.

For 4-mercapto-2-pentanone [FL-no: 12.264], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3-mercapto-2-pentanone [FL-no: 12.031] from a 90-day study in rats (Morgareidge, 1971b) provides an adequate margin of safety (> 1 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For 2-mercaptoanisole [FL-no: 12.139], the NOEL of 0.51 mg/kg bw per day for the structurally related substance 2-mercaptomethylbenzene [FL-no: 12.027] from a 90-day study in rats (Posternak et al., 1969) provides an adequate margin of safety (at least 25 500) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethane-1,1-dithiol [FL-no: 12.293], the NOEL of 125 mg/kg bw per day for one hydrolysis product, acetaldehyde [FL-no: 05.001], from a 28-day study in rats (Til et al., 1988) and the NOEL of 6.5 mg/kg bw per day for the other hydrolysis product, hydrogen sulfide, from a 90-day inhalation study in rats (Chemical Industry Institute of Technology, 1983) provide adequate margins of safety (625 million and > 32 million, respectively) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For dimercaptomethane [FL-no: 12.243], the NOEL of 15 mg/kg bw per day for one hydrolysis product, formaldehyde, from a 2-year study in rats (Til et al., 1989) and the NOEL of 6.5 mg/kg bw per day for the other hydrolysis product, hydrogen sulfide, from a 90-day inhalation study in rats (Chemical Industry Institute of Technology, 1983) provide adequate margins of safety (75 million and > 32 million, respectively) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For bis(1-mercaptopropyl)sulfide [FL-no: 12.284], the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2,3-butanedithiol [FL-no: 12.022] from a 90-day study in rats (Morgareidge, 1974b) provides an adequate margin of safety (70 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethyl methyl disulfide [FL-no: 12.153], the NOEL of 7.3 mg/kg bw per day for the structurally related substance propyl disulfide [FL-no: 12.014] from a 90-day study in rats (Posternak et al., 1969) provides an adequate margin of safety (> 14 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances ethyl propyl disulfide [FL-no: 12.126], methyl isopentyl disulfide [FL-No. 12.294], amyl methyl disulfide [FL-no: 12.253], butyl ethyl disulfide [FL-no: 12.254] and diethyl disulfide [FL-no: 12.012], because they are all simple disulfides. For these structurally related substances, the NOEL of 7.3 mg/kg bw per day provides adequate margins of safety in the range of > 14 million to >

36 million in relation to the currently estimated intakes of these substances from use as flavouring agents.

For allyl propyl disulfide [FL-no: 12.021], the NOEL of 4.6 mg/kg bw per day for the structurally related substance diallyl trisulphide [FL-no: 12.009] from a 90-day study in rats (Morgareidge and Oser, 1970d) provides an adequate margin of safety (> 4 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethyl propyl trisulphide [FL-no: 12.256], the NOEL of 4.8 mg/kg bw per day for the structurally related substance dipropyl trisulphide [FL-no: 12.023] from a 90-day study in rats (Morgareidge and Oser, 1970c) provides an adequate margin of safety (24 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substance diethyl trisulphide [FL-no: 12.114], because it is also a trisulphide. The NOEL of 4.8 mg/kg bw per day provides an adequate margin of safety of 24 000 for this substance in relation to the currently estimated level of intake from use as a flavouring agent.

For 3,5-diethyl-1,2,4-trithiolane [FL-no: 15.049], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3,5-dimethyl-1,2,4-trithiolane [FL-no: 15.025] from a 91-day study in rats (BIBRA, 1976) provides an adequate margin of safety (at least 190 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For the mixture of 3,6-diethyl-1,2,4,5-tetrathiane (approximately 55 %) and 3,5-diethyl-1,2,4-trithiolane (approximately 45 %) [FL-no: 12.274], the NOEL of 0.3 mg/kg bw per day for the structurally related substance 3-methyl-1,2,4-trithiane [FL-no: 15.036] from a 90-day study in rats (Mondino, 1981a) provides an adequate margin of safety (30 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For thioacetic acid [FL-no: 12.199], the NOEL of 6.5 mg/kg bw per day for the structurally related substance ethyl thioacetate [FL-no: 12.018] from a 91-day study in rats (Shellenberger, 1970b) provides an adequate margin of safety (> 900 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances *S*-methyl propanethioate [FL-no: 12.165], *S*-isopropyl 3-methylbut-2-enethioate [FL-no: 12.134], allylthio hexanoate [FL-no: 12.275] and *S*-ethyl 2-acetylaminoethanethioate (No. 1680), because they are all thioesters and related acids. For these structurally related substances, the NOEL of 6.5 mg/kg bw per day provides adequate margins of safety in the range of > 3 million to > 32 million in relation to their currently estimated levels of intake from their use as flavouring agents.

For 1-p-menthene-8-thiol [FL-no: 12.085] a NOEL of 0.56 mg/kg bw per day was reported in a 90-day study in rats treated with cyclopentanethiol [FL-no: 12.029] only at that dose (Morgareidge and Oser, 1970b).

For the four thiols with oxygenated side-chains [FL-no: 12.038, 12.137, 12.138, 12.145], NOELs are available for three substances (1.9 mg/kg bw per day for 2-mercapto-3-butanol [FL-no: 12.024] (JECFA No. 546), 2.8 mg/kg bw per day for alpha-methyl-beta-hydroxypropyl alpha-methyl-beta-mercaptopropyl sulfide [FL-no: 12.036] (JECFA No. 547), and 1.9 mg/kg bw per day for 3-mercapto-2-pentanone [FL-no: 12.031] (JECFA No. 560)). These NOELs were considered to provide adequate safety margins for the flavouring agents in this subgroup.

No adequate NOEL was available for benzyl methyl sulphide and methyl phenyl sulphide [FL-no: 12.077 and 12.162] or a related substance, therefore no adequate margin of safety can be provided. Therefore evaluation of the substance proceeds with step B5.

Step B5.

Four substances, di-isopentyl thiomalate [FL-no: 12.108], propyl propanethiosulfonate [FL-no: 12.272], benzyl methyl sulphide [FL-no: 12.077] and methyl phenyl sulphide [FL-no: 12.162] were

evaluated at this step of the Procedure. The currently estimated daily per capita intakes of all four substances are below 1.5 microgram/person per day in Europe. Applying the criteria for Step B5 outlined in Annex 5 of the evaluations published after its forty-ninth meeting, the Committee concluded that the use of these substances as flavouring agents at their currently estimated levels of intake poses no safety concern.

4.2. Application of the Procedure to Aliphatic and Alicyclic Mono-, Di-, Tri-, and Polysulphides with or without Additional Oxygenated Functional Groups by EFSA in FGE.08Rev3 (EFSA, 2010w)

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach.

For two of the candidate substances, 2-methylpropane-2-thiol [FL-no: 12.174] (subgroup III) and methyl methanethiosulphonate [FL-no: 12.159] (the only substance in subgroup X), there is an indication of a genotoxic potential *in vitro*. Therefore, in the absence of further genotoxicity data, the Panel concluded that the Procedure could not be applied to these two substances, and not to the two structurally related candidate substances, 2-methylbutane-2-thiol [FL-no: 12.172] (subgroup III) and 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057] (subgroup VII).

For four candidate substances, 3-mercaptooctanal [FL-no: 12.268] (subgroup III), 3-mercaptodecanal [FL-no: 12.269] (subgroup III), methanedithiol diacetate [FL-no: 12.271] (subgroup VIII) and 3,5-dimethyl-1,2-dithiolane-4-one [FL-no: 12.295] (subgroup V) no data on use as flavouring substances in Europe are available. Therefore, no intakes in Europe can be estimated and accordingly the Panel concluded that the Procedure could not be applied to these four substances.

For the safety evaluation of the remaining 62 candidate substances from chemical groups 20 and 30 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the 62 substances evaluated through the Procedure are summarised in Table 2a (FGE.08Rev3 (EFSA, 2010w)).

Step 1

The candidate substances were classified following the procedure established by Cramer et al. (Cramer et al., 1978). For the 62 candidate substances evaluated through the Procedure, 39 substances were classified into structural class I. Further 17 substances were classified into structural class II. The final six substances were classified into structural class III.

Step 2

Step 2 requires consideration of whether metabolic pathways exist to metabolise the candidate substances to innocuous products at the expected levels of intake. The candidate substances may be biotransformed to reactive metabolites, such as thiols, sulphoxides and sulphones and, in consequence, they are not predicted to be metabolised to innocuous products. Therefore, the evaluation of all 62 candidate substances proceeds via the B-side of the Procedure scheme (Annex I of FGE.08Rev3) (FGE.08Rev3 (EFSA, 2010w)).

Step B3

The 39 substances in structural class I have estimated European daily *per capita* intakes ranging from 0.0012 to 6.1 microgram, which is below the threshold of concern of 1800 microgram/person/day. The 17 substances evaluated through the Procedure in structural class II have estimated European daily *per capita* intakes ranging from 0.0024 to 2.4 microgram, which is below the threshold of concern for class II of 540 microgram/person/day. The six substances in structural class III have estimated European daily *per capita* intakes ranging from 0.012 to 6.1 microgram, which is below the threshold

of concern for class III of 90 microgram/person/day. Accordingly, all 62 candidate substances proceed to step B4 of the Procedure.

Step B4

No adequate studies on candidate substances are available. Repeated-dose toxicity studies are available on some supporting substances, which, with very few exceptions, have been carried out testing only one dose, giving rise to no observed adverse effects. The results of adequate studies on supporting substances show a relatively high degree of variability in the reported No Observed Adverse Effect Levels (NOAELs), ranging from 0.06 to 250 mg/kg bw/day.

The 18 candidate substances in subgroup I can be represented by the supporting substance dimethyl sulfide [FL-no:12.006], for which an adequate 90-day subchronic study is available, indicating that no adverse effects were produced by the highest oral dose tested (250 mg/kg body weight (bw)/day), which can be considered a NOAEL. The combined estimated daily *per capita* intake of 10 microgram for the 18 candidate substances in subgroup I corresponds to 0.17 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.5×10^6 can be calculated. The 18 candidate substances in subgroup I are accordingly not expected to be of safety concern at the estimated levels of intake.

Within subgroup II, no adequate toxicity study from which a NOAEL could be established was available, neither on the candidate substances nor on supporting substances. Therefore, the Panel concluded that additional data are required for the three cyclic sulphides in subgroup II [FL-no: 12.120, 15.102 and 15.125].

Within subgroup III, adequate 90-day subchronic studies are available for four supporting substances, 2-mercapto-3-butanol [FL-no: 12.024], cyclopentanethiol [FL-no: 12.029], 2-, 3- and 10-mercaptopinane [FL-no: 12.035] and 2,6-(dimethyl)thiophenol [FL-no: 12.082], which can be considered representative of the eight candidate substances evaluated through the Procedure in this subgroup. In the four studies, no adverse effects were produced by the highest oral dose tested ranging from 0.06 up to 0.7 mg/kg bw/day. By adopting a conservative approach the lowest value (0.06 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily *per capita* intake of 0.9 microgram for the eight candidate substances evaluated through the Procedure in subgroup III corresponds to 0.015 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 4×10^3 can be calculated. The eight candidate substances in subgroup III, evaluated through the Procedure are accordingly not expected to be of safety concern at the estimated levels of intake.

The candidate substance in subgroup IV can be represented by two supporting substances, butane-2,3-dithiol [FL-no: 12.022] and octane-1,2-dithiol [FL-no: 12.034], for which adequate 90-day subchronic studies are available. In the two studies, no adverse effects were produced by the almost identical highest oral doses tested, that is 0.7 mg/kg bw/day, which can be considered a NOAEL. The estimated daily *per capita* intake of 0.3 microgram for the one candidate substance in subgroup IV corresponds to 0.005 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.4×10^5 can be calculated. The candidate substance in subgroup IV is accordingly not expected to be of safety concern at the estimated level of intake.

Within subgroup V, adequate 90-day subchronic studies are available for two supporting substances dicyclohexyl disulfide [FL-no: 12.028] and benzyl methyl disulfide [FL-no: 12.068], which can be considered representative of the three candidate substances in this subgroup evaluated through the Procedure. In the two studies, no adverse effects were produced by the highest oral dose tested: 0.23 and 1.15 mg/kg bw/day. By adopting a conservative approach, the lowest value (0.23 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily *per capita* intake of 0.54 microgram for the three candidate substances evaluated through the Procedure in subgroup V corresponds to 0.009 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 2.6×10^5 can be calculated. The three candidate substances in subgroup V are accordingly not expected to be of safety concern at the estimated levels of intake.

Within subgroup VI, no adequate toxicity study from which a NOAEL could be established was available, neither on the candidate substances nor on supporting substances. Therefore, the Panel concluded that additional data are required for the eight tri-, tetra- and polysulphides in subgroup VI [FL-no: 12.093, 12.094, 12.097, 12.100, 12.112, 12.116, 12.164 and 12.167].

Within subgroup VII, adequate 90-day subchronic studies are available for two supporting substances, 3,5-dimethyl-1,2,4-trithiolane [FL-no: 15.025] and 2-methyl-4-propyl-1,3-oxathiane [FL-no: 16.030], which can be considered representative for 10 of the remaining 11 candidate substances in this subgroup to be evaluated through the Procedure. For the candidate substance [FL-no: 15.134] the structural similarity to the two supporting substances for which there is a NOAEL was not considered to be sufficient. In the two 90-day studies, no adverse effects were produced by the highest oral dose tested: 0.44 and 1.88 mg/kg bw/day. By adopting a conservative approach, the lowest value (0.44 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily per capita intake of 2,6 microgram for these 10 candidate substances in subgroup VII corresponds to 0.043 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 10^5 can be calculated. The Panel is aware of a study that has been performed with a substance [FL-no: 15.006] which is structurally related to 2,5-Dihydroxy-1,4-dithiane [FL-no: 15.134]. However, this 90-day study from 1973 by Cox et al. was not available to the Panel and the validity of the derived NOAEL from this study could not be assessed. Consequently the evaluation of [FL-no: 15.134] cannot be finalised. The remaining 10 candidate substances in subgroup VII, evaluated through the Procedure, are not expected to be of safety concern at the estimated levels of intake.

Within subgroup VIII, an adequate 90-day subchronic study is available for one supporting substance, ethyl thioacetate [FL-no: 12.018], which can be considered representative of the eight candidate substances evaluated through the Procedure in this subgroup. In the study, no adverse effects were produced by the highest oral dose tested: 6.63 mg/kg bw/day. Therefore, the NOAEL is concluded to be 6.63 mg/kg bw per day for ethyl thioacetate. The combined estimated daily *per capita* intake of 2.4 microgram for the eight candidate substances in subgroup VIII corresponds to 0.04 microgram/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.7×10^5 can be calculated. The eight candidate substances in subgroup VIII are accordingly not expected to be of safety concern at the estimated levels of intake.

Within subgroup IX, no data are available for the candidate substance ethanethioic acid [FL-no: 12.199]. Therefore, the Panel concluded that additional data are required for the candidate substance in subgroup IX.

Within subgroup XI, no adequate toxicity study from which a NOAEL could be established was available on the candidate substance. No supporting substances are available. Therefore the Panel concluded that additional data are required for the candidate substance in subgroup XI [FL-no: 15.007].

The conclusion from step B4 is that for the 48 candidate substances belonging to subgroups I, III, IV, V, VII and VIII, and evaluated through the Procedure, adequate NOAELs exist for structurally related substances providing adequate margins of safety at the estimated levels of intake. Therefore, these candidate substances are not expected to be of safety concern at the levels of exposure estimated by the MSDI approach. For the three candidate substances belonging to subgroup II [FL-no: 12.120, 15.102 and 15.125], the eight candidate substances belonging to subgroup VI [FL-no: FL-no: 12.093, 12.094, 12.097, 12.100, 12.112, 12.116, 12.164 and 12.167] and for one candidate substance belonging to subgroup VII [FL-no: 15.134] and the candidate substance of subgroup IX [FL-no: 12.199] and the candidate substance belonging to subgroup XI [FL-no: 15.007] additional toxicity data are required. The substance in subgroup X is not evaluated through the Procedure due to concern for genotoxicity.

The stepwise evaluations of the substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA, 2010w).

4.3. EFSA Considerations

The 47 JECFA evaluated simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group are distributed into eight subgroups of structurally related substances. The subgrouping is the same as used in FGE.08Rev3. See Section 1.1.2 and Table 4.3.1. Subgrouping of substances in FGE.08Rev3 is shown in Annex II, Table 4.3.2.

Within this group there are seven tertiary thiols, 8-mercapto-p-menthan-3-one, p-menth-1-ene-8-thiol, 3-mercapto-3-methylbutan-1-ol, 3-mercaptobutyl formate, 4-methoxy-2-methylbutane-2-thiol, 4-mercapto-4-methyl-2-pentanol and 1-mercapto-p-menthan-3-one [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259]. These substances are structurally related to two tertiary thiols 2-methylbutane-2-thiol and 2-methylpropane-2-thiol [FL-no: 12.172 and 12.174], and the tertiary thiol resulting from hydrolysis of 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057] evaluated in FGE.08Rev3 and for which the Panel had concern with respect to genotoxicity. The Panel further noted that the substance propyl propanethiosulphonate [FL-no: 12.272] in the present FGE shows structural similarity to a substance evaluated in FGE.08Rev3, methyl methanethiosulphonate [FL-no: 12.159], for which there was concern with respect to genotoxicity due to structural alikeness with the direct acting carcinogen methyl methanesulphonate.

Accordingly, for eight substances, the Panel concluded that in line with the conclusions for [FL-no: 12.172, 12.174 and 16.057] and [FL-no: 12.159] in FGE.08Rev3, the following seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] and the sulphonate [FL-no: 12.272], should not be evaluated using the Procedure until adequate genotoxicity data become available. Furthermore, for three of these substances [FL-no: 12.137, 12.138 and 12.145] no exposure estimate (MSDI) for the EU can be calculated due to lack of tonnage data.

Table 4.3.1 Subgrouping (as in FGE.08Rev3) of the 47 Simple Aliphatic and Aromatic Sulfides and Thiols in FGE.91Rev1 (Due to considerations stated in Section 3.3, subgroup III has been subdivided into IIIa – Monothiols and subgroup IIIb – Tertiary Monothiols).

Table 4.3.1 The subgrouping of the 47 Simple Aliphatic and Aromatic Sulfides and Thiols

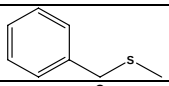
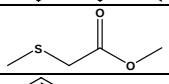
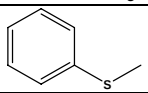
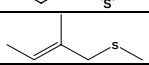
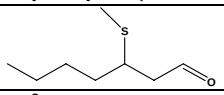
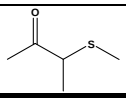
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
I Acyclic sulphides In FGE.08Rev3 this subgroup was represented by supporting substance [FL-no: 12.006], for which an adequate NOAEL is available (Butterworth et al, 1975b).			
12.077 460	Benzyl methyl sulphide		II
12.146 1691	Methyl (methylthio)acetate		I
12.162 459	Methyl phenyl sulphide		II
12.265 1683	2-Methyl-1-methylthio-2-butene		I
12.273 1692	3-(Methylthio)heptanal		I
12.285 1688	3-Methylthio-2-butanone		I

Table 4.3.1 The subgrouping of the 47 Simple Aliphatic and Aromatic Sulfides and Thiols

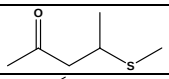
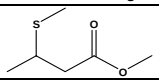
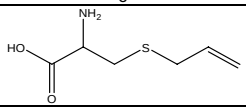
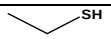
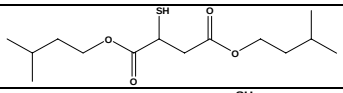
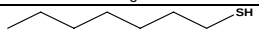
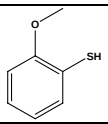
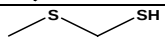
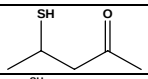
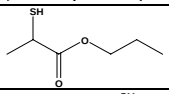
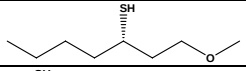
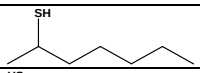
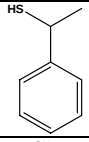
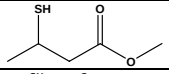
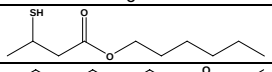
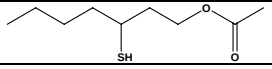
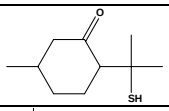
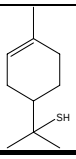
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
12.286 1689	4-Methylthio-2-pentanone		I
12.287 1690	Methyl 3-(methylthio)butanoate		I
17.036 1710	S-allyl-L-cysteine		III
IIIa Monothiols In FGE.08Rev3 this subgroup was represented by supporting substances [FL-no: 12.024, 12.029, 12.035, 12.082] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al, 1974a; Morgareidge&Oser, 1970b; Oser, 1966; Peano et al, 1981).			
12.017 1659	Ethanethiol		I
12.108 1672	Di-isopentyl thiomalate		III
12.130 1663	Heptane-1-thiol		I
12.139 1666	2-Mercaptoanisole		III
12.242 1675	Methylthiomethylmercaptan		I
12.264 1670	4,2-Thiopentanone		I
12.267 1667	Propyl-2-mercaptopropionate		I
12.276 1671	(S)-1-Methoxy-3-heptanethiol		I
12.288 1664	Heptan-2-thiol		I
12.289 1665	1-Phenylethylmercaptan		II
12.290 1674	Methyl-3-mercaptobutanoate		I
12.292 1704	Hexyl 3-mercaptobutanoate		I
12.297 1708	3-Mercaptoheptyl acetate		I
IIIb Tertiary Monothiols Concern for genotoxic potential identified for this subgroup.			
12.038 561	8-Mercapto-p-menthan-3-one		II
12.085 523	p-Menth-1-ene-8-thiol		II

Table 4.3.1 The subgrouping of the 47 Simple Aliphatic and Aromatic Sulfides and Thiols

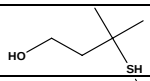
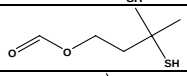
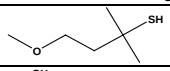
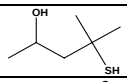
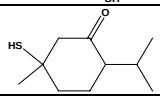
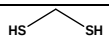
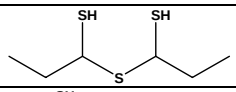
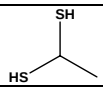
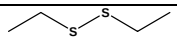
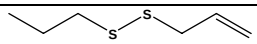
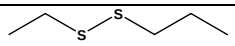
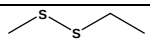
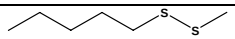
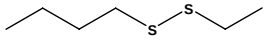
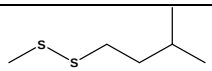
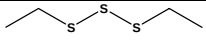
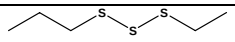
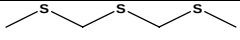
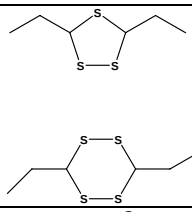
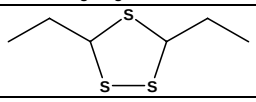
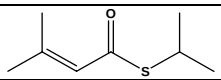
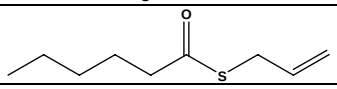
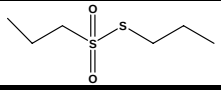
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
12.137 544	3-Mercapto-3-methylbutan-1-ol		I
12.138 549	3-Mercapto-3-methylbutyl formate		I
12.145 548	4-Methoxy-2-methylbutane-2-thiol		I
12.252 1669	4-Mercapto-4-methyl-2-pentanol		I
12.259 1673	1-Mercapto-p-menthan-3-one		II
IV Dithiols In FGE.08Rev3 this subgroup was represented by supporting substances [FL-no: 12.022, 12034] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al, 1974c; Cox et al, 1974d).			
12.243 1661	Dimercaptomethane		I
12.284 1709	bis(1-Mercaptopropyl)sulfide		I
12.293 1660	Ethane-1,1-dithiol		I
V Acyclic and cyclic disulphides In FGE.08Rev3 this subgroup was represented by supporting substances [FL-no: 12.028, 12.068] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al, 1974e; Gallo et al 1976a).			
12.012 1699	Diethyl disulfide		I
12.021 1700	Allyl propyl disulfide		II
12.126 1694	Ethyl propyl disulfide		I
12.153 1693	Methyl ethyl disulfide		I
12.253 1697	Amyl methyl disulfide		I
12.254 1698	Butyl ethyl disulfide		I
12.294 1696	Isopentyl methyl disulfide		I
VI Acyclic polysulphides No adequate NOAEL exists for this subgroup.			
12.114 1701	Diethyl trisulfide		I
12.256 1695	Ethyl propyl trisulfide		I
VII Mono-, di-, tri-, and poly-sulphides with thioacetal structure In FGE.08Rev3 this subgroup was represented by supporting substances [FL-no: 15.009; 15.025; 15.034; 15.036; 16.030] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (BIBRA, 1976; Mondino et al, 1981a; Griffiths et al, 1979; Cox et al, 1973b).			
12.240 1684	2,4,6-Trithiaheptane		I

Table 4.3.1 The subgrouping of the 47 Simple Aliphatic and Aromatic Sulfides and Thiols

FL-no JECFA-no	EU Register name	Structural formula	Structural Class
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		II
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		II
VIII Thioesters In FGE.08Rev3 this subgroup was represented by supporting substances [FL-no: 12.018] for which an adequate NOAEL exists (Shellenberger, 1970b).			
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		I
12.275 1681	Allylthio hexanoate		II
X Sulphoxides/sulphones and sulphonates Concern for genotoxic potential identified for the substance in this subgroup.			
12.272 1702	Propyl propanethiosulfonate		III

The Panel agrees with JECFA that the remaining 39 candidate substances in this FGE can be evaluated through the Procedure.

For five [FL-no: 12.108, 12.077, 12.114, 12.162 and 12.256] of these 39 substances the Panel did not agree with the way the JECFA carried out the evaluation.

Three substances, di-isopentyl thiomalate [FL-no: 12.108], benzyl methyl sulphide [FL-no: 12.077] and methyl phenyl sulphide [FL-no: 12.162]), have been cleared by JECFA at step B5 (the MSDI < 1.5 μg per person per day). This approach is not supported by the Panel (see Section 1.1.2). However, for [FL-no: 12.108], which belongs to subgroup IIIa, NOAELs ranging from 0.06 to 0.7 mg/kg bw/day are available based on adequate 90-day sub-chronic studies on the four supporting substances in subgroup III of FGE.08Rev3 (IIIa of thisFGE). These NOELs have been reported for 3-mercapto-2-butanol [FL-no: 12.024], cyclopentanethiol [FL-no: 12.029], 2-,3- and 10-mercaptopinane [FL-no: 12.035] and 2,6-(dimethyl)-thiophenol [FL-no: 12.082] (Peano et al., 1981; Morgareidge and Oser, 1970b; Oser, 1966; Cox et al., 1974a). Using the lowest NOEAL of 0.06 mg/kg bw and an EU MSDI of 0.012 μg/*capita* a margin of safety of 3 x 10^5 can be calculated. The Panel considered this margin of safety sufficiently large to conclude no safety concern at the estimated level of intake at step B4 of the Procedure.

Because benzyl methyl sulphide and methyl phenyl sulphide [FL-no: 12.077 and 12.162] are sulphides the Panel has allocated them to subgroup I, despite the fact that there are no other sulphides with aromatic substituents in this subgroup. Thus, no structurally related substance occurs in this subgroup which can provide an adequate NOAEL to evaluate [FL-no: 12.077 and 12.162]. However, sulphides can be considered metabolites of thiols. For subgroup III (thiols), a common biotransformation pathway is methylation of the thiol to the corresponding sulphide followed by S-oxidation and elimination (FGE.08Rev3). Therefore, toxicity data of thiols can be used for the evaluation of sulphides assuming that the toxicity of thiols is higher than the toxicity of sulphides because of the greater reactivity of the thiol group as compared to the sulphide group. For the thiols in subgroup III, 90 days studies are available for four substances, including one with an aromatic ring (2,6-

(dimethyl)thiophenol [FL-no: 12.082]). For this substance a NOAEL of 0.43 mg/kg bw/day was derived. Using this NOAEL of 0.43 mg/kg bw/day and the MSDIs of 0.09 µg/*capita*/day for benzyl methyl sulphide and of 0.012 µg/*capita*/day for methyl phenyl sulphide, respectively, margins of safety of 2.8 x 10^5 and 2.1 x 10^6, are derived. The Panel considered these margins of safety sufficiently large to conclude no safety concern at the estimated level of intake at step B4 of the Procedure.

No NOAEL could be identified for subgroup VI, Acyclic tri- and polysulphides or for sufficiently structurally related substances. Accordingly the Panel concluded at step B4 (contrary to the JECFA) that further data are required for the trisulphides [FL-no: 12.114 and 12.256].

For in total 37 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, 12.264, 12.265, 12.267, 12.273, 12.274, 12.275, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297, 15.049 and 17.036] the Panel concluded in line with the JECFA: "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach at step B4 of the Procedure.

5. Conclusion

This consideration deals with 47 simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group which are in the Register and which were evaluated by the JECFA at its 53rd and 68th meetings.

The Panel concluded that these 47 substances are structurally related to the aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in the Flavouring Group Evaluation 08, Revision 3 (FGE.08Rev3). The 47 JECFA evaluated substances are distributed into eight subgroups of structurally related substances. The subgrouping is the same as used in FGE.08Rev3.

Eight substances (the seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] and the sulphonate [FL-no: 12.272]) are structurally related to substances in FGE.08Rev3 {[FL-no: 12.172 and 12.174] (subgroup III, monothiols), [FL-no: 16.057] (subgroup VII, mono-, di-, tri- and polysulphides with thioacetal structure) and [FL-no: 12.159] (subgroup X, sulphoxides/sulphones and sulphonates)} for which the Panel had identified concerns with respect to genotoxicity. Consequently these substances were not evaluated using the Procedure and adequate genotoxicity data are needed. Furthermore, for three of these substances [FL-no: 12.137, 12.138 and 12.145] no exposure estimate (MSDI) for the EU can be calculated due to lack on tonnage data for use in the EU.

The Panel agrees with the JECFA that the remaining 39 of the 47 substances can be evaluated through the Procedure.

For five substances [FL-no: 12.077, 12.108, 12.114, 12.162 and 12.256] the Panel did not agree with the application of the Procedure by the JECFA for the following reasons:

The Panel did not agree with the application of the procedure by the JECFA for substances [FL-no: 12.077, 12.108 and 12.162], which have been cleared by the JECFA at step B5 (the MSDI < 1.5 µg person per day). However, the Panel considers that adequate NOAELs exist to evaluate these substances and concluded at step B4 "No safety concern at the estimated levels of intake".

For the trisulphides [FL-no: 12.114 and 12.256], contrary to the JECFA, the Panel concluded that no adequate NOAEL exists at step B4 of the Procedure and that additional toxicity data are required.

For in total 37 substances, the Panel concluded in line with the JECFA: "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach at step B4 of the Procedure.

For 36 substances, use levels have been provided by the Industry. The mTAMDI figures calculated for five substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural classes. For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For 11 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267, 12.272 and 17.036] for which use levels have not been provided, use levels are needed to calculate the mTAMDI values in order to identify those flavouring substances that need more refined exposure assessment.

In order to determine whether the conclusion for the 39 JECFA evaluated substances, for which the Panel concluded that they could be evaluated through the Procedure, can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria and identity are available for 35 substances evaluated through the Procedure. Information on the composition of the stereoisomeric mixture is lacking for three substances [FL-no: 12.274, 12.284 and 15.049] and information on solubility in ethanol for [FL-no: 12.162] is missing.

Thus, for five substances [FL-no: 12.114, 12.256, 12.274, 12.284, and 15.049] evaluated through the Procedure, the Panel has reservations (additional toxicity data are required [FL-no: 12.114 and 12.256], or information on the composition of stereoisomeric mixture is needed [FL-no: 12.274, 12.284 and 15.049]).

For 34 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, 12.264, 12.265, 12.267, 12.273, 12.275, 12.276, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297 and 17.036] the Panel agrees with the JECFA conclusion "No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach."

TABLE 1 SPECIFICATION SUMMARY

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Simple Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2008c)

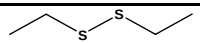
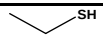
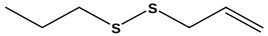
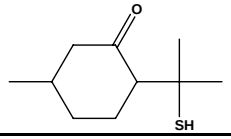
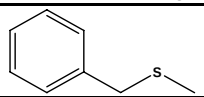
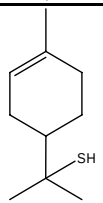
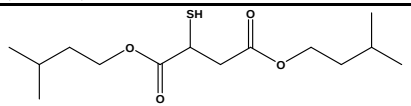
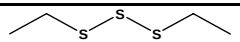
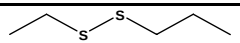
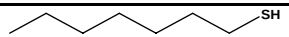
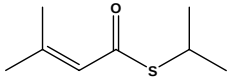
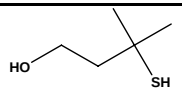
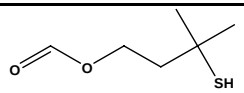
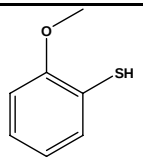
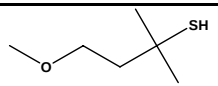
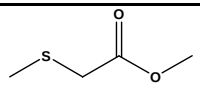
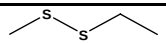
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.012 1699	Diethyl disulfide		 533 110-81-6	Liquid $C_4H_{10}S_2$ 122.24	Practically insoluble or insoluble Soluble	152 IR MS 95 %	1.502-1.508 0.990-0.996	(EFFA, 2004ak).
12.017 1659	Ethanethiol		 546 75-08-1	Liquid C_2H_6S 62.13	Slightly soluble Soluble	35 IR NMR MS 95 %	1.425-1.431 0.833-0.839	(EFFA, 2004ak).
12.021 1700	Allyl propyl disulfide		4073 600 2179-59-1	Liquid $C_6H_{12}S_2$ 148.28	Practically insoluble or insoluble Soluble	66 (13 hPa) NMR MS 95 %	1.497-1.517 0.999-1.005	(EFFA, 2004ak).
12.038 561	8-Mercapto-p-menthan-3-one 6)		3177 11789 38462-22-5	Liquid $C_{10}H_{18}OS$ 186.31	Insoluble Soluble	120 (13 hPa) IR 97 %	1.492-1.509 0.995-1.010	(JECFA, 1999c; California Department of Pest. Regulation, 1987).
12.077 460	Benzyl methyl sulfide		3597 766-92-7	Liquid $C_8H_{10}S$ 138.23	Slightly soluble Soluble	197 IR 98 %	1.563-1.573 1.015-1.020	(JECFA, 1999c; EFFA, 2011k).
12.085 523	p-Menth-1-ene-8-thiol 6)		3700 71159-90-5	Liquid $C_{10}H_{18}S$ 170.31	Slightly soluble	58 (0.4 hPa) IR 98 %	1.504 0.948 (20°)	(JECFA, 1999c).
12.108 1672	Di-isopentyl thiomalate		 11454 68084-03-7	Solid $C_{14}H_{26}O_4S$ 290.42	Practically insoluble or insoluble Soluble	425 50 NMR MS 95 %	n.a. n.a.	Specifications (EFFA, 2004ak). Racemate (EFFA, 2010a).
12.114 1701	Diethyl trisulfide		4029 11451 3600-24-6	Liquid $C_4H_{10}S_3$ 154.3	Practically insoluble or insoluble Soluble	217 NMR MS 95 %	1.556-1.560 1.121-1.231	(EFFA, 2006u).
12.126 1694	Ethyl propyl disulfide		4041 11478	Liquid $C_5H_{12}S_2$	Practically insoluble or insoluble	180	1.483-1.493 0.943-0.953	(EFFA, 2006u).

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Simple Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2008c)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
			30453-31-7	136.27	Soluble	IR NMR MS 95 %		
12.130 1663	Heptane-1-thiol		4259 11485 1639-09-4	Liquid $C_7H_{16}S$ 132.26	Practically insoluble or insoluble Soluble	175 IR NMR MS 95 %	1.497-1.503 0.840-.0846	(EFFA, 2004ak).
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		4260 34365-79-2	Liquid $C_8H_{14}OS$ 158.26	Practically insoluble or insoluble Soluble	236 NMR 95 %	1.486-1.492 1.006-1.012	(EFFA, 2004ak).
12.137 544	3-Mercapto-3-methylbutan-1-ol		3854 34300-94-2	Liquid $C_5H_{12}OS$ 120.2	Soluble Soluble	186 (950 hPa) NMR MS 96 %	1.480-1.490 0.989 (20°)	(JECFA, 1999c).
12.138 549	3-Mercapto-3-methylbutyl formate		3855 50746-10-6	Liquid $C_6H_{12}O_2S$ 148.22	Soluble Soluble	181 IR 95 %	1.462-1.472 1.03	(JECFA, 1999c).
12.139 1666	2-Mercaptoanisole		4159 11880 7217-59-6	Liquid C_7H_8OS 140.2	Practically insoluble or insoluble Soluble	227 IR NMR MS 95 %	1.589-1.595 1.137-1.149	(EFFA, 2006u).
12.145 548	4-Methoxy-2-methylbutane-2-thiol		3785 94087-83-9	Liquid $C_6H_{14}OS$ 134.24	Insoluble Soluble	59 IR 98 %		RI 7), SG 8) (JECFA, 1999c).
12.146 1691	Methyl (methylthio)acetate		4003 11525 16630-66-3	Liquid $C_4H_8O_2S$ 120.2	Practically insoluble or insoluble Soluble	145 IR NMR MS 98 %	1.464-1.466 1.105-1.115	(EFFA, 2006u).
12.153 1693	Methyl ethyl disulfide		4040 11470 20333-39-5	Liquid $C_3H_8S_2$ 108.22	Practically insoluble or insoluble Soluble	137 IR NMR MS 80 %	1.410-1.418 1.015-1.029	Min. Assay value 80 %. Secondary components are 7-8 % diethyl sulfide and 8-10 % dimethyl sulfide (EFFA, 2006u; EFFA, 2011k).

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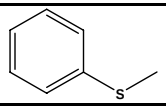
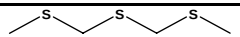
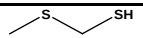
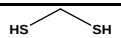
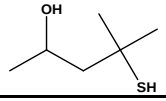
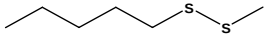
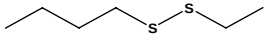
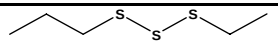
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.162 459	Methyl phenyl sulfide		3873 11533 100-68-5	Liquid C_7H_8S 124.21	Insoluble	188-193 IR 98 %	1.532-1.551 0.958-0.968	(JECFA, 1999c; EFFA, 2011k).
12.240 1684	2,4,6-Trithiaheptane		4214 6540-86-9	Liquid $C_4H_{10}S_3$ 154.32	Slightly soluble Soluble	255 IR NMR MS 95 %	1.444-1.445 1.540-1.550	(EFFA, 2006u).
12.242 1675	Methylthiomethylmercaptan		4185 29414-47-9	Liquid $C_2H_6S_2$ 94.2	Soluble Soluble	40 (2.7 hPa) NMR 97 %	1.552-1.556 1.040-1.046	(EFFA, 2006u).
12.243 1661	Dimercaptomethane		4097 6725-64-0	Liquid CH_4S_2 80.17	Soluble Soluble	118 NMR 95 %	1.578-1.584 0.827-0.831	(EFFA, 2006u).
12.252 1669	4-Mercapto-4-methyl-2-pentanol 6)		4158 31539-84-1	Liquid $C_6H_{14}OS$ 134.26	Soluble Soluble	51 (0.1 hPa) NMR 98 %	1.463-1.468 1.154-1.158	(EFFA, 2006u).
12.253 1697	Amyl methyl disulfide		4025 72437-68-4	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	198-202 IR NMR MS 97 %	1.485-1.495 0.943-0.953	Specifications (EFFA, 2006u). Minimum assay (97 %) (EFFA, 2010a).
12.254 1698	Butyl ethyl disulfide		4027 63986-03-8	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	202 IR NMR MS 90 %	1.492-1.502 0.950-0.968	Minimum assay (90 %). Secondary components diethyl disulfide (2-3%) and dibutyl disulfide (5-6 %) (EFFA, 2006u; EFFA, 2010a).
12.256 1695	Ethyl propyl trisulfide		4042 31499-70-4	Liquid $C_5H_{12}S_3$ 168.34	Practically insoluble or insoluble Soluble	234-237 IR NMR MS 98 %	1.549-1.559 1.070-1.087	Minimum assay (98 %). Secondary components diethyl trisulfide (20-30 %) and dipropyl trisulfide (20-30 %) (EFFA, 2006u; EFFA, 2010a).

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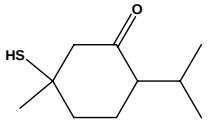
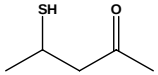
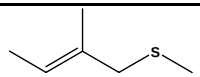
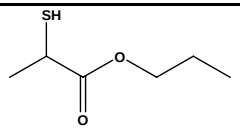
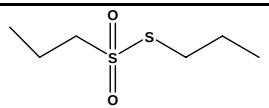
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.259 1673	1-Mercapto-p-menthan-3-one 6)		4300 29725-66-4	Liquid $C_{10}H_{18}OS$ 186.31	Practically insoluble or insoluble Soluble	122 (1.3 hPa) NMR 89 %	1.487-1.497 0.989-0.999	Minimum assay (89 %) (EFFA, 2006u). Secondary components are piperitone (8-9 %) and alpha-terpineol (1-2 %) (California Department of Pest. Regulation, 1987).
12.264 1670	4,2-Thiopentanone		4157 92585-08-5	Liquid $C_5H_{10}OS$ 118.00	Insoluble Soluble	258-260 IR NMR MS 95 %	1.437-1.443 1.154-1.158	Specifications (Flavour Industry, 2006x). Racemate (EFFA, 2010a).
12.265 1683	2-Methyl-1-methylthio-2-butene		4173 89534-74-7	Liquid $C_6H_{12}S$ 116.23	Very slightly soluble Soluble	78 (100hPa) IR NMR MS 99.3 %	1.471 0.861	Industry has informed: 99.3 % (E)-isomer, 0.2 % (Z)-isomer, 0.2 % 1-methylthio-2-propanone, 0.1 % methyl 2-methyl-2-butenoate, 0.2 % unknown. Register name to be changed to (E)-2-Methyl-1-methylthio-2-butene (Flavour Industry, 2007j).
12.267 1667	Propyl-2-mercaptopropionate		4207 19788-50-2	Liquid $C_6H_{12}O_2S$ 148.23	Very slightly soluble Soluble	193 IR NMR MS 97.3 %	1.4497 1.018	Specifications (Flavour Industry, 2007j). Racemate (EFFA, 2010a).
12.272 1702	Propyl propanethiosulfonate		4263 1113-13-9	Liquid $C_6H_{14}O_2S_2$ 182.31	Sparingly soluble Soluble	113 IR NMR MS 95 %	1.485 1.121	(Flavour Industry, 2007j).

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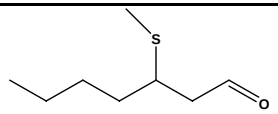
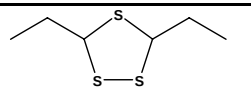
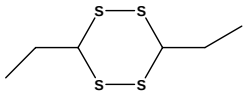
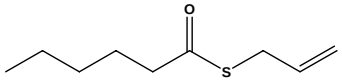
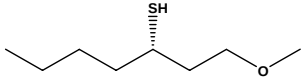
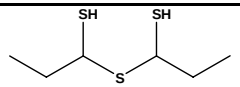
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.273 1692	3-Methyl thioheptanal		4183 51755-70-5	Liquid $C_8H_{16}OS$ 160.28	Insoluble Soluble	95-96 IR NMR MS 92 %	1.469-1.475 0.943-0.947	Specifications (Flavour Industry, 2006x). Register name to be changed to 3-(Methyl thio)heptanal. Racemate. Minimum assay (92 %). Secondary component 2-(E)-heptanal (5–7 %) (EFFA, 2010a).
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides	 	4094	Liquid $C_6H_{12}S_4/C_6H_{12}S_3$ 212.43	Insoluble Soluble	64-70 (1.3 hPa) NMR MS 95 % (1 % solution)	1.447-1.453 0.948-0.952	Mixture of CASrn 54644-28-9 (FL-no: 15.049) and 54717-12-3. Molecular weight: 212.43/180.36. (Flavour Industry, 2006x). Mixture of three diastereo-isomers (EFFA, 2010a). Composition of mixture to be specified.
12.275 1681	Allylthio hexanoate		4076 156420-69-8	Liquid $C_9H_{16}OS$ 172.29	Insoluble Soluble	195-196 IR NMR MS 98 %	1.473-1.479 0.930-0.934	(Flavour Industry, 2006x).
12.276 1671	(S)-1-Methoxy-3-heptanethiol		4162 400052-49-5	Liquid $C_8H_{18}OS$ 162.30	Slightly soluble Soluble	203.8 IR NMR MS 99 %	1.456-1.457 0.908-0.908	(Flavour Industry, 2007i; EFFA, 2011k).
12.284 1709	bis(1-Mercaptopropyl)sulphide		 53897-60-2	Liquid $C_6H_{14}S_3$ 182	Insoluble Soluble	225-226(101hPa) IR NMR > 98 %	1.542-1.552 1.077-1.087	Specifications (Flavour Industry, 2004m). Mixture of diastereo-isomers (EFFA, 2010a). Composition of mixture to be specified.

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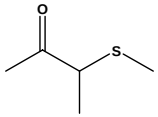
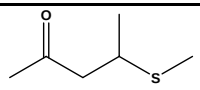
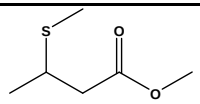
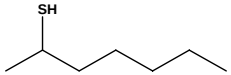
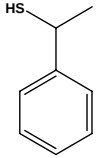
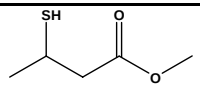
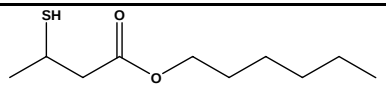
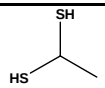
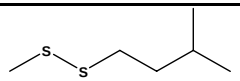
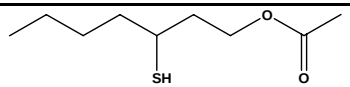
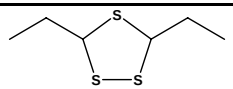
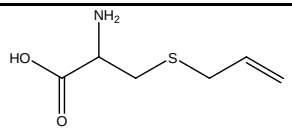
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.285 1688	3-Methylthio-2-butanone		 53475-15-3	Liquid $C_5H_{10}OS$ 118.2	Slightly soluble Soluble	160 IR NMR 97 %	1.468-1.4774 0.992-0.998	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.286 1689	4-Methylthio-2-pentanone		 143764-28-7	Liquid $C_6H_{12}OS$ 132.22	Very slightly soluble Soluble	183 NMR MS 98 %	1.468-1.472 0.969-0.979	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.287 1690	Methyl 3-(methylthio)butanoate		4166 207983-28-6	Liquid $C_6H_{12}O_2S$ 148.22	Very slightly soluble Soluble	193 NMR 98 %	1.459-1.465 1.034-1.040	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.288 1664	Heptan-2-thiol		 628-00-2	Liquid $C_7H_{16}S$ 132.27	Slightly soluble Soluble	164 NMR 98 %	1.442-1.448 0.832-0.838	Racemate (Flavour Industry, 2005h).
12.289 1665	1-Phenylethylmercaptan		 6263-65-6	Liquid $C_8H_{10}S$ 138.23	Practically insoluble or insoluble Soluble	199 NMR MS 98 %	1.552-1.558 1.001-1.007	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.290 1674	Methyl-3-mercaptobutanoate		4167 54051-19-3	Liquid $C_5H_{10}O_2S$ 134.20	Practically insoluble or insoluble Soluble	172 NMR 98.5 %	1.451-1.461 1.052-1.058	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.292 1704	Hexyl 3-mercaptobutanoate		4136 796857-79-9	Liquid $C_{10}H_{20}O_2S$ 204.33	Practically insoluble or insoluble Soluble	268 NMR 98 %	1.459-1.465 0.949-0.955	Specifications (Flavour Industry, 2005h). Racemate (EFFA, 2010a).
12.293 1660	Ethane-1,1-dithiol		 69382-62-3	Liquid $C_2H_6S_2$ 94.2	Soluble Soluble	120 NMR 99 %	1.360-1.366 0.830-0.834	Product is a 1% solution of ethane-1,1-dithiol, purity 99 % min, in ethanol.

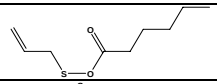
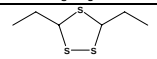
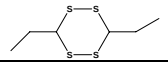
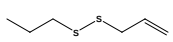
Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Simple Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2008c)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments / References for specifications
12.294 1696	Isopentyl methyl disulfide		4168 72437-56-0	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	184-200 NMR 95 %	1.516-1.522 0.995-1.001	(Flavour Industry, 2005h).
12.297 1708	3-Mercaptoheptyl acetate		4289 548774-80-7	Liquid $C_9H_{18}O_2S$ 190.30	Slightly soluble Soluble	242 IR NMR MS 99.9 %	1.4605-1.4607 0.9826-0.9830	Specifications (Flavour Industry, 2007j; EFFA, 2011k). Racemate (EFFA, 2010a).
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		4030 54644-28-9	Liquid $C_6H_{12}S_3$ 180.35	Practically insoluble or insoluble Soluble	77 (0.1 hPa) NMR 95 %	1.558-1.570 1.147-1.160	Specifications (EFFA, 2006u). Mixture of three diastereo-isomers (EFFA, 2010a). Composition of mixture to be specified.
17.036 1710	S-allyl-L-cysteine		4322 21593-77-1	Solid $C_6H_{11}NOS$ 161.22	Moderate soluble Slightly soluble	 214-216 IR NMR MS 95%	1.542 1.191	(Flavour Industry, 2007j).

1) Solubility in water, if not otherwise stated.
2) Solubility in 95 % ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.
6) Stereoisomeric composition not specified.
7) RI: Missing refractive index.
8) SG: Missing specific gravity.

TABLE 2 GENOTOXICITY DATA

Table 2.1: Summary of Genotoxicity Data of Simple Aliphatic and Aromatic Sulfides and Thiols evaluted by the JECFA (JECFA, 2008b)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
12.275 1681	Allylthio hexanoate		Reverse Mutation	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	5[a], 15[a], 50, 150,500, 1500 or 5000 microg/plate	Negative[b]	(King and Harnasch, 2002a)
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		Reverse Mutation[c]	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	0.1, 0.316, 1, 3, 16 or10 microg/plate	Negative[b]	(Uhde, 2005)
			Reverse Mutation	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	0.1, 0.316, 1, 3, 16 or10 microg/plate	Negative[b]	(Uhde, 2005)
							
12.021 1700	Allyl propyl disulfide		Reverse Mutation[d]	*S.typhimurium* TA97, TA98, TA100, TA102, TA1535, TA1537	Up to 333 microg/plate	Negative[b]	(Zeiger et al., 1988)
	Allyl propyl disulfide [e]		Reverse Mutation[f]	*S.typhimurium* TA100	Not specified	Negative[b]	(Eder et al., 1982b)
	Allyl propyl disulfide [g]		Reverse Mutation[f]	*S.typhimurium* TA100	0.0015 – 0.15 microl/ml 1.5 – 150 microg/ml	Negative[b]	(Eder et al., 1980)

[a] Concentration tested in the absence of metabolic activation.

[b] With and without metabolic activation.

[c] Plate incorporation method.

[d] Preincubation method.

[e] Mixture of 32 % allyl propyl disulfide, 31 % propyl disulfide and 32 % allyl disulfide.

[f] Liquid suspension method.

[g] Mixture of 31 % allyl propyl disulfide, 37 % propyl disulfide and 32 % allyl disulfide.

[h] Calculated bease on specific gravity of allyl propyl disulfide (0.999-1.005 g/ml).

Substances listed in brackets are the JECFA evaluated supporting substances in FGE.08Rev3

Table 2.2: GENOTOXICITY (*in vitro*) EFSA / FGE.08Rev3 (EFSA, 2010w)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
Subgroup I – Acyclic Sulphides						
(Diallyl sulfide [12.088])	Ames test	S. *typhimurium* TA100	0.004 – 0.44 µg/ml	Negative (±S9)	(Eder et al., 1982a)	Review. No details on method and results reported. Only TA100 used.
	Sister chromatid exchange	Chinese hamster ovary cells	200 - 600 µg/ml	Positive[1]	(Musk et al., 1997)	Limited quality of study. Insufficiently reported.
	Chromosomal aberrations	Chinese hamster ovary cells	200 - 600 µg/ml	Positive [1]	(Musk et al., 1997)	Limited quality of study. Insufficiently reported.
Di-(1-propenyl)-sulfid (mixture) [12.298]	*Ames test*	S. *typhimurium* TA98, TA100, TA102, TA1535, TA1537	1 – 100 µg/plate	Negative[1]	(Stien, 2005c)	
Subgroup III – Monothiols						
2-Methylpropane-2-thiol [12.174]	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10000 µg/plate	Negative (±S9)	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Forward mutational MLTK assay	L5178Y/tk+/- mouse lymphoma cells	1000 µg/ml	Positive (-S9) Negative (+S9)	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Sister chromatid exchange	Chinese hamster ovary cells	1350 µg/ml	Negative (+S9)[2]	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
(Allyl mercaptan [12.004])	Modified Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.005 – 1.5 µl/ml (4.6 – 1400 µg/ml)	Negative (±S9)	(Eder et al., 1980)	Acceptable quality.
(Benzyl mercaptan [12.005])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
(2-Mercaptopropionic acid [12.039])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
(Benzenethiol [12.080])	Ames test	S. *typhimurium* TA98, TA100	25 – 500 µg/plate	Negative (±S9)	(LaVoie et al., 1979)	Insufficient quality (only two strains were used, and all doses -except the lowest dose - were toxic).
Subgroup IV – Dithiols						
(1,2-Ethanedithiol [12.066])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 doses up to 5000 µg/plate	Negative (±S9)	(Phillips Petroleum Company, 1990b)	Validity cannot be fully evaluated (only abstract provided).
	Sister chromatid exchange	Chinese hamster ovary cells	0.5 - 50 µg/ml	Positive (±S9)	(Pence et al., 1982)	Acceptable quality.
	Forward mutational assay	L5178Y/tk+/- mouse lymphoma cells	150 µg/ml	Positive (-S9)	(Pence et al., 1982)	Positive only at cytotoxic concentrations.
	Forward mutational assay	L5178Y/tk+/- mouse lymphoma cells	1 µg/ml	Negative (+S9)	(Pence et al., 1982)	Insufficiently documented.
Subgroup V – Acyclic disulphides						
(Allyl disulfide [12.008])	Modified Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.0015 – 0.15 µg/ml	Negative (±S9)	(Eder et al., 1980)	Acceptable quality.
	Sister chromatid exchange	Chinese hamster ovary cells	2 - 25 µg/ml	Negative (-S9)	(Musk et al., 1997)	Limited quality. Insufficiently reported.
	Chromosomal aberrations	Chinese hamster ovary cells	2 - 25 µg/ml	Positive (-S9)	(Musk et al., 1997)	Limited quality. Insufficiently reported.
(Dimethyl disulfide [12.026])	Ames test	S. *typhimurium* TA98, TA100, TA102	0.000011 – 1.1 mmol/plate (1.04 - 104000 µg/plate)	Negative (±S9)	(Aeschbacher et al., 1989)	Limited quality (only 3 strains used).
(Phenyl disulfide [12.043])	Ames test	S. *typhimurium* TA98, TA100,	3.6 mg/plate (3600	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.

Table 2.2: GENOTOXICITY (*in vitro*) EFSA / FGE.08Rev3 (EFSA, 2010w)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
		TA1535, TA1537, TA1538	µg/plate)			
(Benzyl disulfide [12.081])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
Dibutyl disulfide [12.111]	Forward mutational assay	Mouse lymphoma cells	NR	Negative (-S9)	(Dooley et al., 1987)	Validity cannot be fully evaluated (only abstract provided).
Subgroup VIII – Thioesters						
(Methylthio 2-(acetyloxy)propionate [12.203])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, *E. Coli* WP2uvrA	0.156-5.0 mg/plate (156-5000 µg/plate	Negative (±S9)	(Watanabe and Morimoto, 1989a)	Acceptable quality.
(Methylthio 2-(propionyloxy) propionate [12.227])	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, *E. Coli* WP2uvrA	0.156 – 5.0 mg/plate (156 - 5000 µg/plate)	Negative (±S9)	(Watanabe and Morimoto, 1989b)	Acceptable quality.
Subgroup X – Sulfoxides/Sulphones and Sulphonates						
Methyl methane-thiosulfonate [12.159]	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538, TA2637	0.6 – 60 µg/plate	Negative (-S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Ames test	S. *typhimurium* TA98, TA100, TA1535, TA1537, TA1538, TA2637	2 – 600 µg/plate	Negative (+S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Ames test	S. *typhimurium* TA98, TA100, TA2637	0.6 – 60 µg/plate	Negative (-S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Ames test	S. *typhimurium* TA98, TA100, TA2637	0.6 – 200 µg/plate	Negative (+S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Ames test	S. *typhimurium* TA98, TA100, TA2637	NR	Negative[3]	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Ames test	S. *typhimurium* TA98, TA100, TA2637	0.6 – 200 µg/plate	Negative[4]	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Yeast assay	S. *cerevisiae* Strain D7	1– 300 µg/ml	Negative (±S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
	Yeast assay	S. *cerevisiae* Haploid strain N123	1– 100 µg/ml	Negative (±S9)	(Dorange et al., 1983)	Test is not appropriate for antimicrobial agents[6].
(Methylsulfinyl methane [12.175]) (synonym: dimethylsulfoxid, DMSO)	Ames test	S. *typhimurium* TA97, TA98, TA100	100000 – 300000 µg/plate	Negative (±S9)	(Brams et al., 1987)	Insufficient method (3 strains and 3 concentrations only).
	Ames test	S. *typhimurium* TA97, TA98, TA100, TA1535, TA1537	100 – 10000 µg/plate	Negative (±S9)	(Zeiger et al., 1992)	Acceptable quality.
	Ames test	S. *typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1538, *E. Coli* WP2	0.1 – 0.4 ml/plate (100000 - 400000 µg/plate)	Negative (-S9)	(Hakura et al., 1993)	Good quality study.
	Ames test	S. *typhimurium* TA1537, TA2637, *E. Coli* WP2uvrA	0.1 – 0.4 ml/plate (100000 - 400000 µg/plate)	Positive (-S9) [5]	(Hakura et al., 1993)	Good quality study. Positive at high doses with reduced bacterial survival. Doses routinely used in Ames test were negative.

NR: Not reported.

[1] With and without metabolic activation at clearly cytotoxic concentrations.

[2] A statistically significant increase in the number of SCEs per chromosome was seen at 1350 µg/ml and the 450 µg/ml dose level in the presence of metabolic activation; but no significant increase was seen in the remaining dose levels, and no dose level showed a two fold increase in SCEs; therefore, t-butyl mercaptan is not considered to be mutagenic.

[3] With 100 µl/plate fecalase.

[4] With 100 µl/plate S9 metabolic activation and 100 µl/plate fecalase. Negative results reported after 2 days of incubation. Results for TA98 test strain were positive after 5 days of incubation.

[5] Positive results obtained at doses where lethal toxicity was observed. Negative results obtained at doses routinely used in Ames test.

[6] Thiosulfonates in general, and methyl methane thiosulfonate in particular, are non-specific antimicrobial agents that are active at low concentrations on prokaryotic bacteria, as well as on yeast and other eukaryotic fungi. This was even pointed out by Dorange et al. (1983). Therefore bacterial test systems and yeast assays are not appropriate to evaluate genotoxicity of thiosulfonates.

Substances listed in brackets are the JECFA-evaluated substances supporting substances in FGE.08Rev3

Table 2.3: GENOTOXICITY (*in vivo*) EFSA / FGE.08Rev3 (EFSA, 2010w)

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
Subgroup I – Acyclic Sulphides							
(Allyl sulfide [12.088])	*In vivo* mouse micronucleus test	Mouse	gavage	0.33 – 0.67 mM/kg (38 – 77 mg/kg)[1]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup III – Monothiols							
(2-Mercaptopropionic acid [12.039])	*In vivo* Basc test	Drosophila	dietary route	10 mM (1061 µg/ml)	Negative	(Wild et al., 1983)	Limited quality (insufficiently documented). The article compiles results obtained with 76 substances in 3 test systems.
Subgroup V – Acyclic disulphides							
(Allyl disulfide [12.008])	*In vivo* mouse micronucleus test	Mouse	gavage	0.33 – 0.67 mM/kg (48 – 98 mg/kg) [1]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup VI – Acyclic polysulphides							
(Diallyl trisulfide [12.009])	*In vivo* mouse micronucleus test	Mouse	gavage	0.33 – 0.67 mM/kg (59 - 120 mg/kg)[1]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup X – Sulphoxides/Sulphones and Sulphonates							
Methyl methane-thiosulfonate [12.159]	*In vivo* gene mutation	*Nicotiana tabacum* seeds	-	2 - 4 mg/ml (2000 - 4000 µg/ml)	Negative	(Dorange et al., 1983)	Heterozygotic seeds were used. After exposure, the seeds were blotted on filter paper and planted in earthenware pots in medium normally used for planting tobacco. The leaves were analysed for alterations indicating genotoxicity. This assay cannot be regarded as standard test.
	In vivo gene mutation	*Nicotiana tabacum* seeds	-	50 – 400 µg/ml	Negative	(Dorange et al., 1983)	Heterozygotic seeds were used. After exposure, the seeds were blotted on filter paper and planted in earthenware pots in medium normally used for planting tobacco. The leaves were analysed for alterations indicating genotoxicity. This assay cannot be regarded as standard test.

[1] Study used a mixture of allyl sulfide, allyl disulfide and ally trisulfide in the respective ratio, 68:20:12.

TABLE 3: SUMMARY OF SAFETY EVALUATIONS

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

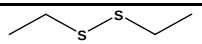
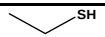
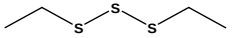
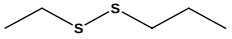
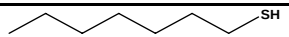
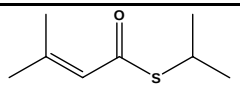
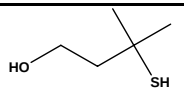
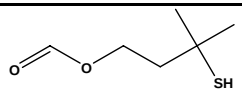
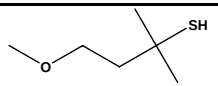
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.012 1699	Diethyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.017 1659	Ethanethiol		0.49 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.114 1701	Diethyl trisulfide		16 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Data must be available on the substance or closely related substances to perform a safety evaluation	Data must be available on the substance or closely related substances to perform a safety evaluation.
12.126 1694	Ethyl propyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.130 1663	Heptane-1-thiol		0.037 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.137 544	3-Mercapto-3-methylbutan-1-ol		ND 2	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.138 549	3-Mercapto-3-methylbutyl formate		ND 0.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.145 548	4-Methoxy-2-methylbutane-2-thiol		ND 0.8	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

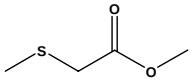
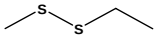
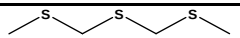
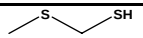
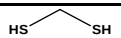
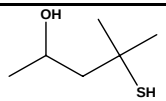
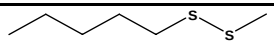
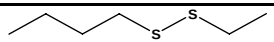
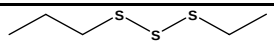
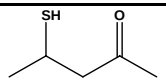
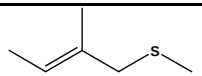
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.146 1691	Methyl (methylthio)acetate		0.24 1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.153 1693	Methyl ethyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.240 1684	2,4,6-Trithiaheptane		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.242 1675	Methylthiomethylmercaptan		0.012 0.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.243 1661	Dimercaptomethane		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.252 1669	4-Mercapto-4-methyl-2-pentanol		0.012 0.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.253 1697	Amyl methyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.254 1698	Butyl ethyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.256 1695	Ethyl propyl trisulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Data must be available on the substance or closely related substances to perform a safety evaluation	Data must be available on the substance or closely related substances to perform a safety evaluation.
12.264 1670	4,2-Thiopentanone		0.12 0.07	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.265 1683	2-Methyl-1-methylthio-2-butene		0.012 0.1	Class I B3: Intake below threshold, B4: Adequate NOAEL	4)	No safety concern at the estimated level of intake based on the MSDI	No safety concern at the estimated level of intake as flavouring substance based

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

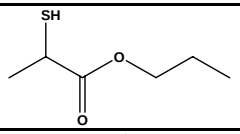
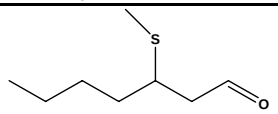
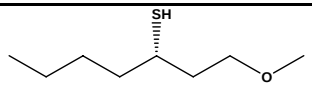
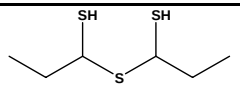
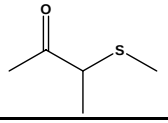
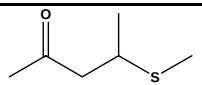
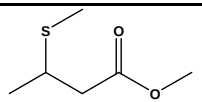
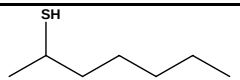
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
				exists		approach	on the MSDI approach. Register name to be changed to (E)-2-Methyl-1-methylthio-2-butene.
12.267 1667	Propyl-2-mercaptopropionate		0.012 0.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.273 1692	3-Methyl thioheptanal		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	Min. Assay value 92 %, secondary components to be specified. Register name to be changed to 3-(Methyl thio)heptanal. No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.276 1671	(S)-1-Methoxy-3-heptanethiol		0.012 2	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.284 1709	bis(1-Mercaptopropyl)sulphide		0.12 0.6	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	Stereoisomeric composition to be specified. Composition of mixture to be specified.
12.285 1688	3-Methylthio-2-butanone		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.286 1689	4-Methylthio-2-pentanone		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.287 1690	Methyl 3-(methylthio)butanoate		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.288 1664	Heptan-2-thiol		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

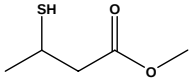
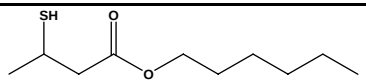
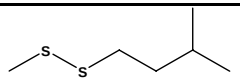
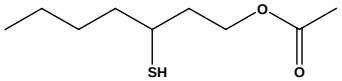
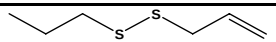
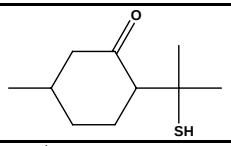
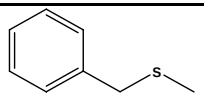
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.290 1674	Methyl-3-mercaptobutanoate		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.292 1704	Hexyl 3-mercaptobutanoate		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.293 1660	Ethane-1,1-dithiol		0.012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.294 1696	Isopentyl methyl disulfide		0.012 ND	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.297 1708	3-Mercaptoheptyl acetate		0.0012 0.01	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.021 1700	Allyl propyl disulfide		0.037 ND	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.038 561	8-Mercapto-p-menthan-3-one		10 2	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.077 460	Benzyl methyl sulfide		0.09 0.02	Class II B3: Intake below threshold, B4: No adequate NOAEL B5: Intake below 1.5 microg/person/day	6)	No safety concern at the estimated level of intake based on the MSDI.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

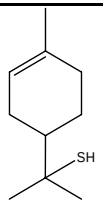
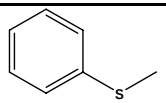
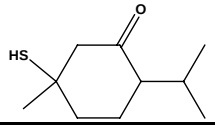
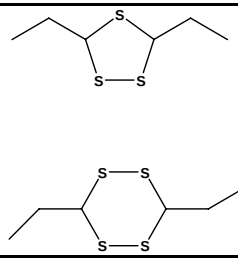
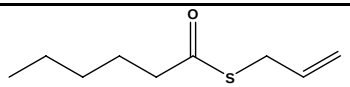
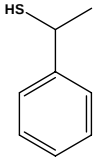
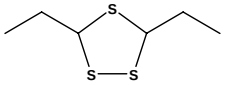
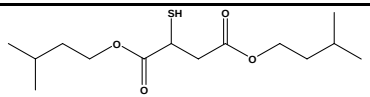
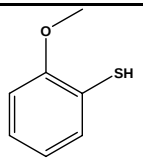
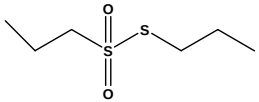
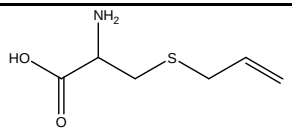
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.085 523	p-Menth-1-ene-8-thiol		0.34 1	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.162 459	Methyl phenyl sulfide		0.012 0.4	Class II B3: Intake below threshold, B4: No adequate NOAEL B5: Intake below 1.5 microg/person/day	6)	No safety concern at the estimated level of intake based on the MSDI.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.259 1673	1-Mercapto-p-menthan-3-one		1.6 ND	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		0.61 ND	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	Composition of mixture to be specified. Stereoisomeric composition to be specified.
12.275 1681	Allylthio hexanoate		0.012 ND	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.289 1665	1-Phenylethylmercaptan		0.012 ND	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Sulfides and Thiols (JECFA, 2000c; JECFA, 2008b)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4), 5) or 6)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		0.61 0.01	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	Stereoisomeric composition to be specified. Composition of mixture to be specified.
12.108 1672	Di-isopentyl thiomalate		0.012 ND	Class III B3: Intake below threshold, B4: No adequate NOAEL B5: Intake below 1.5 microg/person/day	6)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.139 1666	2-Mercaptoanisole		1.5 ND	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
12.272 1702	Propyl propanethiosulfonate		0.012 ND	Class III B3: Intake below threshold, B4: No adequate NOAEL B5: Intake below 1.5 microg/person/day	6)	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available	Due to concern for genotoxicity, the Procedure cannot be applied until adequate genotoxicity data become available.
17.036 1710	S-allyl-L-cysteine		30 2	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
6) Cleared by the JECFA as intake below 1.5 microg/person/day.
ND: not determined.

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

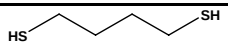
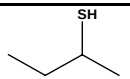
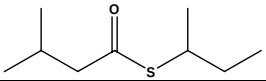
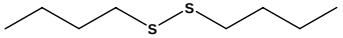
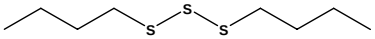
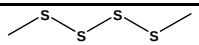
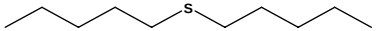
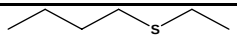
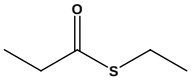
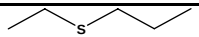
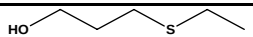
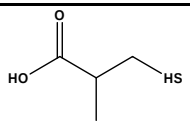
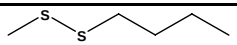
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
12.103	Butane-1,4-dithiol		0.3	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.104	Butane-2-thiol		0.18	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.106	S-2-Butyl 3-methylbutanethioate		0.8	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.111	Dibutyl disulfide		0.37	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.112	Dibutyl trisulfide		0.12	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.116	Dimethyl tetrasulfide		0.016	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.117	Dipentyl sulfide		0.0037	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.124	Ethyl butyl sulfide		0.037	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.125	Ethyl propanethioate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.127	Ethyl propyl sulfide		0.085	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.129	3-(Ethylthio)propan-1-ol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.135	3-Mercapto-2-methylpropionic acid		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.151	Methyl butyl disulfide		0.0061	Class I B3: Intake below threshold,	4)	6)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

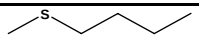
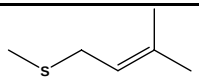
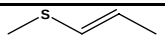
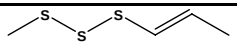
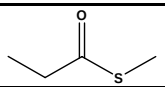
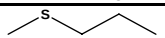
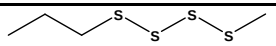
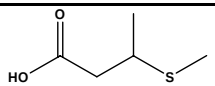
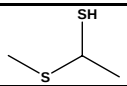
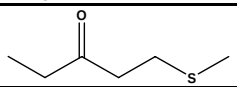
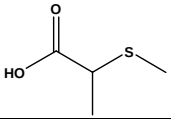
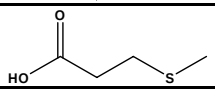
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
				B4: Adequate NOAEL exists			
12.152	Methyl butyl sulfide		0.0024	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.158	Methyl isoprenyl sulfide		0.0012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.163	Methyl prop-1-enyl sulfide		0.0097	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.164	Methyl prop-1-enyl trisulfide		0.0061	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.165 1678	S-Methyl propanethioate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.166	Methyl propyl sulfide		0.0024	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.167	Methyl propyl tetrasulfide		0.0037	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.178	3-(Methylthio)butyric acid		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.180	1-(Methylthio)ethane-1-thiol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.181	1-(Methylthio)pentan-3-one		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.182	2-(Methylthio)propionic acid		0.011	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.183	3-(Methylthio)propionic acid		0.21	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

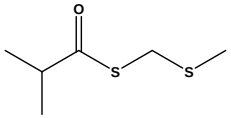
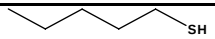
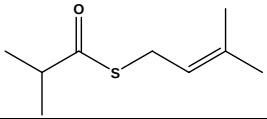
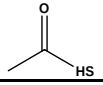
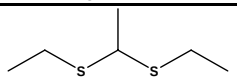
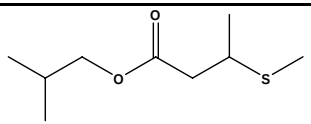
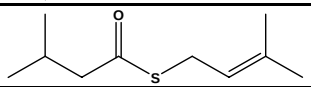
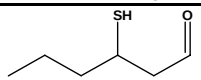
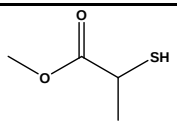
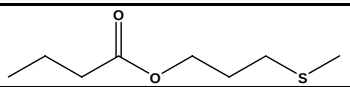
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
12.189	S-(Methylthiomethyl) 2-methylpropanethioate		0.061	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.191 1662	Pentane-1-thiol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.196	S-Prenyl thioisobutyrate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.199 1676	Ethanethioic acid		0.0012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.200	1,1-bis(Ethylthio)-ethane		0.0012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.205	Mercaptoacetaldehyde		0.011	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.214 1677	Isobutyl-3-(methylthio)butyrate		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.221	S-Prenyl thioisopentanoate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.250	3-Mercaptohexanal		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.266	Methyl-2-mercaptopropionate		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	8)	
12.277	3-(Methylthio)propyl butyrate		6.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

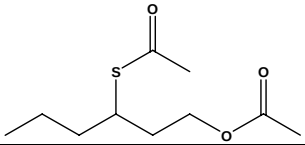
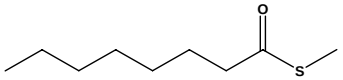
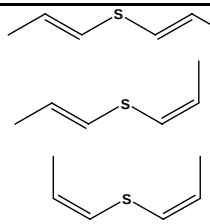
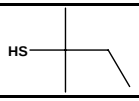
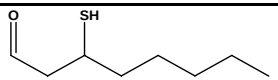
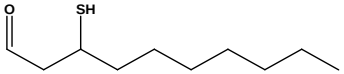
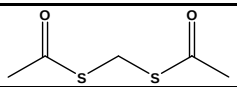
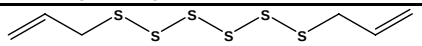
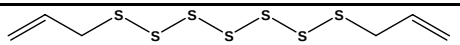
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
12.278	3-Acetyl-mercaptohexyl acetate		1.2	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.282	(S)-Methyl octanethioate		0.24	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.298	Di-(1-propenyl)-sulfid (mixture)		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.172	2-Methylbutane-2-thiol		0.15	Class I No evaluation			a)
12.174	2-Methylpropane-2-thiol		0.0012	Class I No evaluation			a)
12.268	3-Mercaptooctanal			Class I No evaluation			b)
12.269	3-Mercaptodecanal			Class I No evaluation			b)
12.271	Methanedithiol diacetate			Class I No evaluation			b)
12.093	Diallyl hexasulfide		0.011	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.094	Diallyl heptasulfide		0.011	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

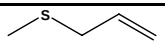
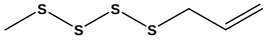
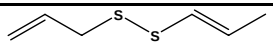
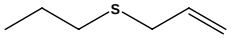
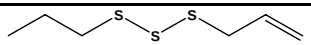
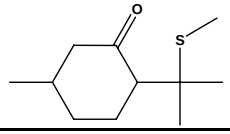
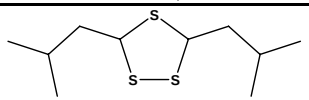
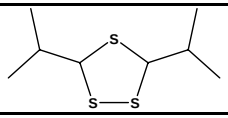
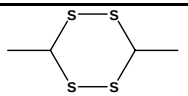
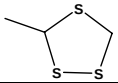
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
12.096	Allyl methyl sulfide		0.99	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.097	Allyl methyl tetrasulfide		0.012	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.098	Allyl prop-1-enyl disulfide		0.17	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
12.099	Allyl propyl sulfide		1.6	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
12.100	Allyl propyl trisulfide		0.12	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.177	8-(Methylthio)-p-menthan-3-one		0.37	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.047	3,5-Di-isobutyl-1,2,4-trithiolane		0.024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.048	3,5-Di-isopropyl-1,2,4-trithiolane		0.0061	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.056	3,6-Dimethyl-1,2,4,5-tetrathiane		0.0024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
15.083	3-Methyl-1,2,4-trithiolane		0.0024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.102	Tetrahydrothiophene		0.024	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

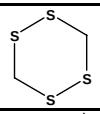
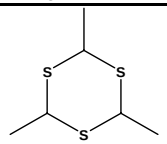
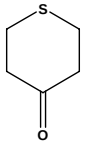
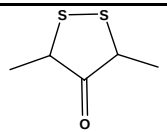
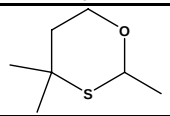
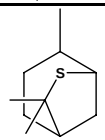
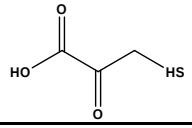
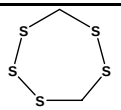
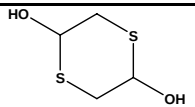
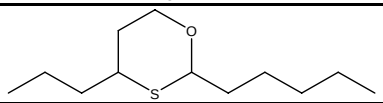
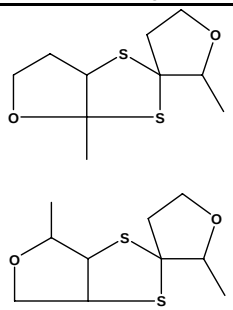
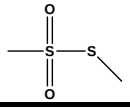
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
15.103	1,2,4,5-Tetrathiane		0.073	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.110	2,4,6-Trimethyl-1,3,5-trithiane		0.0061	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
15.111	1,2,4-Trithiolane		2.4	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.125	4-Tetrahydrothiopyranone		0.12	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.295	3,5-Dimethyl-1,2-dithiolane-4-one			Class II No evaluation			b)
16.057	2,4,4-Trimethyl-1,3-oxathiane		0.0012	Class II No evaluation			a)
12.120 1685	2,8-Epithio-p-menthane		3.7	Class III B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
12.136	3-Mercapto-2-oxopropionic acid		0.24	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) EFSA / FGE.08Rev3

FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
15.081	Lenthionine		0.012	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	6)	
15.134 550	2,5-Dihydroxy-1,4-dithiane		6.1	Class III B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
16.114	2-Pentyl-4-propyl-1,3-oxathiane		0.12	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	7)	
15.007	Spiro(2,4-Dithia-1-methyl-8-oxa-bicyclo[3.3.0]octane-3,3'-(1'- oxa-2'-methyl)-cyclopentane) and spiro(Dithia-6-methyl-7-oxa-bicyclo[3.3.0]octane-3,3'-spiro(2,4-(1'-oxa-2-methyl)cyclopentane)		6.1 2	Class III B4: No adequate NOAEL	Additional data required		
12.159	Methyl methanethiosulfonate		0.061	Class III No evaluation			a)

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.
a) Evaluation deferred pending *in vivo* genotoxicity data.
b) Evaluation deferred pending tonnage data.

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ANNEX I: USE LEVELS AND MTAMDI

Normal and maximum use levels provided by the Flavour Industry (EFFA, 2004ak; EFFA, 2006u; Flavour Industry, 2004m; Flavour Industry, 2005h; Flavour Industry, 2006x; Flavour Industry, 2007i) in accordance with the Commission Regulation (EC) No 1565/2000 (EC, 2000a).

The normal and maximum use levels are shown in Table 2.2.1. Based on these normal use levels mTAMDI figures can be calculated (see Table 2.2.2).

Table 2.2.1 Normal and Maximum use levels (mg/kg) available for JECFA evaluated substances in FGE.91Rev1

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
12.012	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.017	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.021	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.108	0,4 2	0,2 1	0,4 2	0,3 1,5	- -	0,4 2	0,2 1	0,4 2	0,1 0,4	0,1 0,4	- -	- -	0,2 1	0,4 2	0,2 1	0,4 2	1 5	0,2 1
12.114	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,3	0,2 1	0,4 2	0,1 0,5
12.126	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,3	0,2 1	0,4 2	0,1 0,5
12.130	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.134	0,4 2	0,2 1	0,4 2	0,3 1,5	- -	0,4 2	0,2 1	0,4 2	0,1 0,4	0,1 0,4	- -	- -	0,2 1	0,4 2	0,2 1	0,4 2	1 5	2 1
12.139	0,4 2	0,2 1	0,4 2	0,3 1,5	- -	0,4 2	0,2 1	0,4 2	0,1 0,4	0,1 0,4	- -	- -	0,2 1	0,4 2	0,2 1	0,4 2	1 5	0,2 1
12.146	0,4 2	0,2 1	0,4 2	0,3 1,5	- -	0,4 2	0,2 1	0,4 2	0,1 0,4	0,1 0,4	- -	- -	0,2 1	0,4 2	0,2 1	0,4 2	1 5	0,2 1
12.153	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,3	0,2 1	0,4 2	0,1 0,5
12.240	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.242	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.243	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.252	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.253	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.254	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.256	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.259	0,2 1	0,1 0,5	0,2 1	0,2 1	- -	0,2 1	0,1 0,5	0,2 1	0,1 0,2	0,1 0,2	- -	- -	0,1 0,5	0,2 1	0,1 0,5	0,2 1	0,4 2	0,1 0,5
12.264	5 10	5 20	- -	2 10	2 10	- -	- -	10 30	3 20	- -	- -	- -	5 30	- -	1 5	5 10	5 30	- -
12.273	1 10	0,1 1	- -	2 10	2 10	- -	- -	10 50	3 20	- -	- -	- -	2 10	- -	1 10	1 10	5 30	- -
12.274	10 30	5 20	- -	5 20	5 20	- -	- -	10 30	10 20	- -	- -	- -	10 30	- -	1 5	5 10	10 20	- -
12.275	0,4 2	0,4 2	- -	0,2 10	0,2 10	2 10	- -	2,5 12,5	0,3 1,5	0,3 1,5	- -	- -	0,5 5	- -	0,05 0,5	0,25 1,3	0,5 2,5	- -
12.276	0,001 0,01	0,01 0,1	0,001 0,01	0,001 0,01	- -	0,001 0,01	0,002 0,02	0,002 0,02	0,002 0,02	0,002 0,02	- -	- -	0,003 0,03	0,003 0,03	0,001 0,005	0,005 0,05	0,001 0,01	0,001 0,01
12.284	0,05 1,25	0,05 1,25	0,5 12,5	0,05 1,25	0,05 1,25	5 125	1 25	0,5 12,5	0,05 1,25	0,05 1,25	- -	- -	0,05 1,25	- -	5 125	5 125	0,05 1,25	0,05 1,25
12.285	1 5	- -	0,5 0,7	- -	- -	- -	- -	0,8 1	0,2 0,5	- -	- -	- -	1 5	- -	0,5 6	- -	- -	- -
12.286	0,5 0,7	- -	0,5 0,7	- -	- -	- -	- -	0,8 1	2 0,5	- -	- -	- -	- -	- -	0,5 0,6	- -	- -	0,5 1
12.287	0,01 10	0,001 10	0,01 10	0,05 10	- -	- -	- -	- -	0,05 10	- -	0,001 10	- -	0,05 10	- -	0,001 5	- -	0,05 10	0,05 10
12.288	- -	- -	- -	- -	- -	- -	- -	- -	1 5	- -	- -	- -	1 5	- -	4 10	- -	- -	- -
12.289	0,001 0,008	- -	- -	0,001 0,008	- -	0,002 0,025	- -	0,002 0,04	0,002 0,025	- -	- -	- -	0,005 1	- -	0,001 0,02	0,002 0,025	- -	0,1 0,5
12.29	-	-	-	-	-	-	-	-	1	-	-	-	1	-	0,5	-	-	-

Table 2.2.1 Normal and Maximum use levels (mg/kg) available for JECFA evaluated substances in FGE.91Rev1

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
0	-	-	-	-	-	-	-	-	5	-	-	-	5	-	5	-	-	-
12.29	-	-	-	-	-	-	-	-	1	-	-	-	1	-	0,5	-	-	-
2	-	-	-	-	-	-	-	-	5	-	-	-	5	-	5	-	-	-
12.29	-	0,2	-	0,2	-	-	-	-	1	-	-	-	0,6	-	0,2	-	1	-
3	-	2	-	2	-	-	-	-	5	-	-	-	5	-	2	-	5	-
12.29	-	-	0,25	-	-	-	-	0,25	1	-	-	-	-	-	0,5	-	-	0,25
4	-	-	0,5	-	-	-	-	0,5	1,5	-	-	-	-	-	1	-	-	0,5
12.29	0,01	0,1	0,01	0,01	-	0,01	0,02	0,02	0,02	0,02	-	-	0,03	0,03	0,01	0,05	0,01	0,01
7	0,1	1	0,1	0,1	-	0,1	0,2	0,2	0,2	0,2	-	-	0,3	0,3	0,05	0,5	0,1	0,1
15.04	0,2	0,1	0,2	0,2	-	0,2	0,1	0,2	0,1	0,1	-	-	0,1	0,2	0,1	0,2	0,4	0,1
9	1	0,5	1	1	-	1	0,5	1	0,2	0,2	-	-	0,5	1	0,3	1	2	0,5
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2.2.2 Estimated intakes based on the MSDI- and the mTAMDI approach – FGE.91Rev1

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
12.012	Diethyl disulfide	0.012	ND	78	Class I	1800
12.017	Ethanethiol	0.49	ND	78	Class I	1800
12.114	Diethyl trisulfide	16	ND	78	Class I	1800
12.126	Ethyl propyl disulfide	0.012	ND	78	Class I	1800
12.130	Heptane-1-thiol	0.037	ND	78	Class I	1800
12.134	S-Isopropyl 3-methylbut-2-enethioate	0.012	ND	370	Class I	1800
12.137	3-Mercapto-3-methylbutan-1-ol	ND	2	ND	Class I	1800
12.138	3-Mercapto-3-methylbutyl formate	ND	0.1	ND	Class I	1800
12.145	4-Methoxy-2-methylbutane-2-thiol	ND	0.8	ND	Class I	1800
12.146	Methyl (methylthio)acetate	0.24	1	160	Class I	1800
12.153	Methyl ethyl disulfide	0.012	ND	78	Class I	1800
12.240	2,4,6-Trithiaheptane	0.012	ND	78	Class I	1800
12.242	Methylthiomethylmercaptan	0.012	0.1	78	Class I	1800
12.243	Dimercaptomethane	0.012	ND	78	Class I	1800
12.252	4-Mercapto-4-methyl-2-pentanol	0.012	0.1	78	Class I	1800
12.253	Amyl methyl disulfide	0.012	ND	78	Class I	1800
12.254	Butyl ethyl disulfide	0.012	ND	78	Class I	1800
12.256	Ethyl propyl trisulfide	0.012	ND	78	Class I	1800
12.264	4,2-Thiopentanone	0.12	0.07	2000	Class I	1800
12.265	2-Methyl-1-methylthio-2-butene	0.012	0.1	ND	Class I	1800
12.267	Propyl-2-mercaptopropionate	0.012	0.1	ND	Class I	1800
12.273	3-Methyl thioheptanal	0.012	ND	1800	Class I	1800
12.276	(S)-1-Methoxy-3-heptanethiol	0.012	2	1.9	Class I	1800
12.284	bis(1-Mercaptopropyl)sulphide	0.12	0.6	2000	Class I	1800
12.285	3-Methylthio-2-butanone	0.012	ND	320	Class I	1800
12.286	4-Methylthio-2-pentanone	0.012	0.01	430	Class I	1800
12.287	Methyl 3-(methylthio)butanoate	0.012	0.01	9.0	Class I	1800
12.288	Heptan-2-thiol	0.012	0.01	1400	Class I	1800
12.290	Methyl-3-mercaptobutanoate	0.012	0.01	320	Class I	1800
12.292	Hexyl 3-mercaptobutanoate	0.012	0.01	320	Class I	1800
12.293	Ethane-1,1-dithiol	0.012	0.01	230	Class I	1800
12.294	Isopentyl methyl disulfide	0.012	ND	300	Class I	1800
12.297	3-Mercaptoheptyl acetate	0.0012	0.01	19	Class I	1800
12.021	Allyl propyl disulfide	0.037	ND	78	Class II	540
12.038	8-Mercapto-p-menthan-3-one	10	2	ND	Class II	540
12.077	Benzyl methyl sulfide	0.09	0.02	ND	Class II	540
12.085	p-Menth-1-ene-8-thiol	0.34	1	ND	Class II	540
12.162	Methyl phenyl sulfide	0.012	0.4	ND	Class II	540
12.259	1-Mercapto-p-menthan-3-one	1.6	ND	78	Class II	540
12.274	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides	0.61	ND	2200	Class II	540
12.275	Allylthio hexanoate	0.012	ND	430	Class II	540
12.289	1-Phenylethylmercaptan	0.012	ND	14	Class II	540
15.049	3,5-Diethyl-1,2,4-trithiolane	0.61	0.01	78	Class II	540
12.108	Di-isopentyl thiomalate	0.012	ND	160	Class III	90
12.139	2-Mercaptoanisole	1.5	ND	160	Class III	90
12.272	Propyl propanethiosulfonate	0.012	ND	ND	Class III	90
17.036	S-allyl-L-cysteine	30	2	ND	Class III	90

ND: No intake data available

ANNEX II: THE SUBGROUPS IN FGE.08REV3

The 70 candidate substances in FGE.08Rev3 are straight, branched chain or heterogeneous ring aliphatic hydrocarbons containing one or more sulphur atoms. The sulphur-containing functional groups are present as thiols, sulphides or sulphones. Based on their structures, the candidate substances can be subdivided into 11 subgroups (see Table 4.3.2):

Subgroup I Acyclic sulphides: [FL-no: 12.096, 12.099, 12.117, 12.124, 12.127, 12.129, 12.152, 12.158, 12.163, 12.166, 12.177, 12.178, 12.181, 12.182, 12.183, 12.214, 12.277 and 12.298]

Subgroup II Cyclic sulphides: [FL-no: 12.120, 15.102 and 15.125]

Subgroup III Monothiols: [FL-no: 12.104, 12.135, 12.136, 12.172, 12.174, 12.180, 12.191, 12.205, 12.250, 12.266, 12.268 and 12.269]

Subgroup IV Dithiols: [FL-no: 12.103]

Subgroup V Acyclic and cyclic disulphides: [12.098, 12.111, 12.151 and 12.295]

Subgroup VI Acyclic polysulphides: [FL-no: 12.093, 12.094, 12.097, 12.100, 12.112, 12.116, 12.164 and 12.167]

Subgroup VII Mono-, di-, tri- and polysulphides with thioacetal structure: [FL-no: 12.200, 15.047, 15.048, 15.056, 15.081, 15.083, 15.103, 15.110, 15.111, 15.134, 16.057 and 16.114]

Subgroup VIII Thioesters: [FL-no: 12.106, 12.125, 12.165, 12.189, 12.196, 12.221, 12.271, 12.278 and 12.282]

Subgroup IX Thioic acids: [FL-no: 12.199]

Subgroup X Sulphoxides/sulphones and sulphonates: [FL-no: 12.159]

Subgroup XI Cyclic thioketal with fused oxolane ring: [FL-no: 15.007].

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

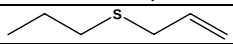
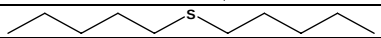
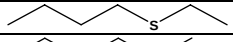
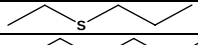
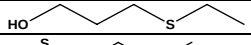
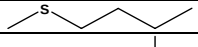
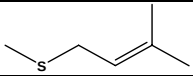
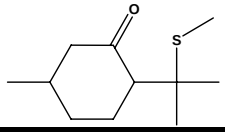
FL-no	EU Register name	Structural formula	Structural Class
I: ACYCLIC SULPHIDES			
12.096	Allyl methyl sulphide		II
12.099	Allyl propyl sulphide		II
12.117	Dipentyl sulphide		I
12.124	Ethyl butyl sulphide		I
12.127	Ethyl propyl sulphide		I
12.129	3-(Ethylthio)propan-1-ol		I
12.152	Methyl butyl sulphide		I
12.158	Methyl isoprenyl sulphide		I
12.163	Methyl prop-1-enyl sulfide		I
12.166	Methyl propyl sulphide		I
12.177	8-(Methylthio)-p-menthan-3-one		II

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

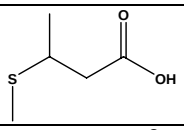
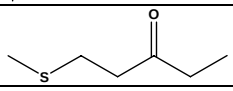
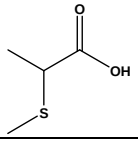
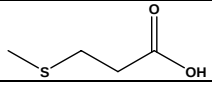
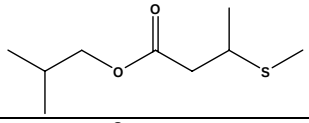
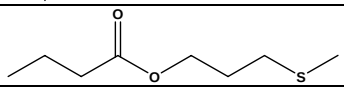
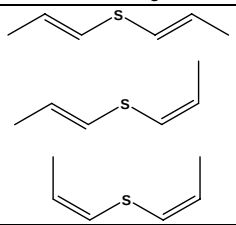
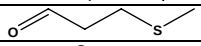
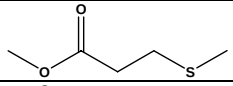
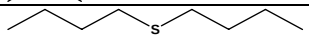
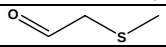
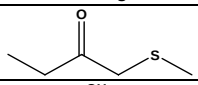
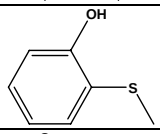
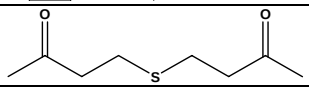
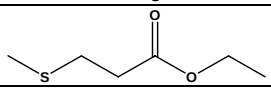
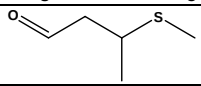
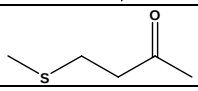
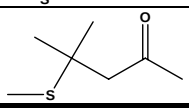
FL-no	EU Register name	Structural formula	Structural Class
12.178	3-(Methylthio)butyric acid		I
12.181	1-(Methylthio)pentan-3-one		I
12.182	2-(Methylthio)propionic acid		I
12.183	3-(Methylthio)propionic acid		I
12.214	Isobutyl-3-(methylthio)butyrate		I
12.277	3-(Methylthio)propyl butyrate		I
12.298	Di-(1-propenyl)-sulfid (mixture)		I
(12.001)	3-(Methylthio)propionaldehyde		I
(12.002)	Methyl 3-(methylthio)propionate		I
(12.006)	Dimethyl sulphide		I
(12.007)	Dibutyl sulphide		I
(12.040)	2-Methylthioacetaldehyde		I
(12.041)	1-(Methylthio)butan-2-one		I
(12.042)	2-(Methylthio)phenol		II
(12.052)	Di-(3-oxobutyl) sulphide		I
(12.053)	Ethyl 3-(methylthio)propionate		I
(12.056)	3-(Methylthio)butanal		I
(12.057)	4-(Methylthio)butan-2-one		I
(12.058)	4-(Methylthio)-4-methylpentan-2-one		I

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

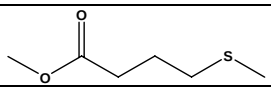
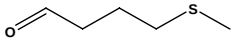
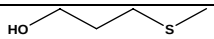
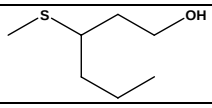
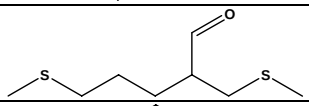
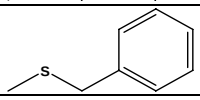
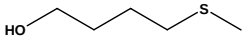
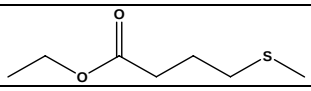
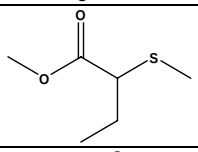
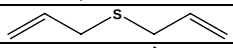
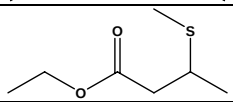
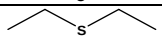
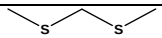
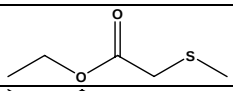
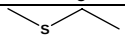
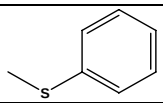
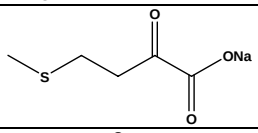
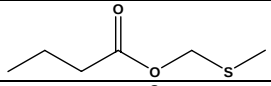
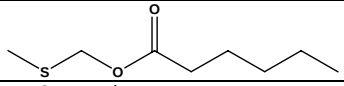
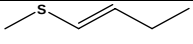
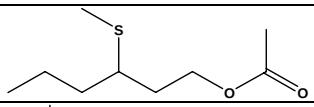
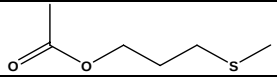
FL-no	EU Register name	Structural formula	Structural Class
(12.060)	Methyl 4-(methylthio)butyrate		I
(12.061)	4-(Methylthio)butanal		I
(12.062)	3-(Methylthio)propan-1-ol		I
(12.063)	3-(Methylthio)hexan-1-ol		I
(12.065)	2,8-Dithianon-4-en-4-carboxaldehyde		I
(12.077)	Benzyl methyl sulphide		II
(12.078)	4-(Methylthio)butan-1-ol		I
(12.084)	Ethyl 4-(methylthio)butyrate		I
(12.086)	Methyl 2-(methylthio)butyrate		II
(12.088)	Diallyl sulphide		II
(12.089)	Ethyl 3-(methylthio)butyrate		I
(12.113)	Diethyl sulphide		I
(12.118)	2,4-Dithiapentane		I
(12.122)	Ethyl 2-(methylthio)acetate		I
(12.154)	Methyl ethyl sulphide		I
(12.162)	Methyl phenyl sulphide		II
(12.176)	4-(Methylthio)-2-oxobutyric acid		III
(12.187)	Methylthiomethyl butyrate		I
(12.188)	Methylthiomethyl hexanoate		I
(12.211)	But-1-enyl methyl sulphide		I
(12.236)	3-(Methylthio)hexyl acetate		I
(12.237)	3-(Methylthio)propyl acetate		I
II: CYCLIC SULPHIDES			

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

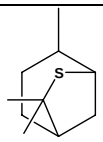
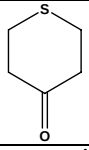
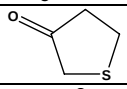
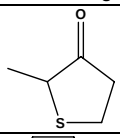
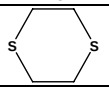
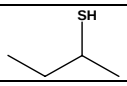
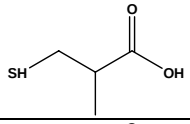
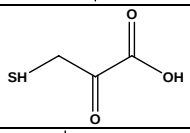
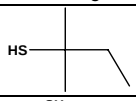
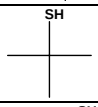
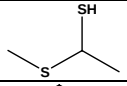
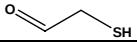
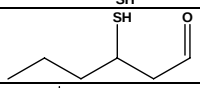
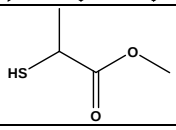
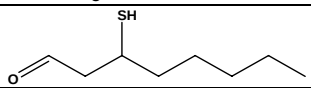
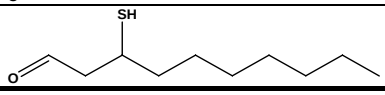
FL-no	EU Register name	Structural formula	Structural Class
12.120	2,8-Epithio-p-menthane		III
15.102	Tetrahydrothiophene		II
15.125	4-Tetrahydrothiopyranone		II
(15.012)	4,5-Dihydrothiophen-3(2H)-one		II
(15.023)	4,5-Dihydro-2-methylthiophene-3(2H)-one		II
(15.066)	1,4-Dithiane		II
III: MONOTHIOLS			
12.104	Butane-2-thiol		I
12.135	3-Mercapto-2-methylpropionic acid		I
12.136	3-Mercapto-2-oxopropionic acid		III
12.172	2-Methylbutane-2-thiol		I
12.174	2-Methylpropane-2-thiol		I
12.180	1-(Methylthio)ethane-1-thiol		I
12.191	Pentane-1-thiol		I
12.205	Mercaptoacetaldehyde		I
12.250	3-Mercaptohexanal		I
12.266	Methyl-2-mercaptopropionate		I
12.268	3-Mercaptooctanal		I
12.269	3-Mercaptodecanal		I

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

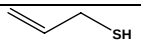
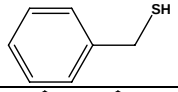
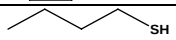
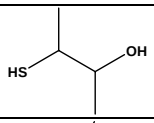
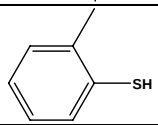
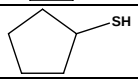
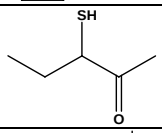
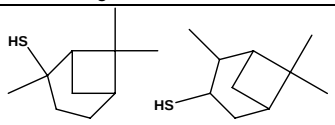
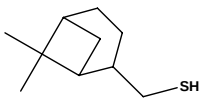
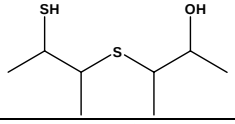
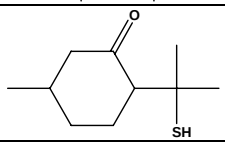
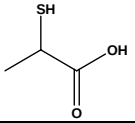
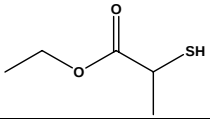
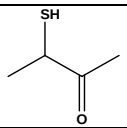
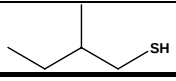
FL-no	EU Register name	Structural formula	Structural Class
(12.003)	Methanethiol		I
(12.004)	Allylthiol		II
(12.005)	Phenylmethanethiol		II
(12.010)	Butane-1-thiol		I
(12.024)	3-Mercaptobutan-2-ol		I
(12.027)	2-Methylbenzene-1-thiol		II
(12.029)	Cyclopentanethiol		II
(12.031)	3-Mercaptopentan-2-one		I
(12.035)	2-,3- and 10-Mercaptopinane	 **2-Mercaptopinane** **3-Mercaptopinane**  **10-Mercaptopinane**	II
(12.036)	3-[(2-Mercapto-1-methylpropyl)thio]butan-2-ol		I
(12.038)	8-Mercapto-p-menthan-3-one		II
(12.039)	2-Mercaptopropionic acid		I
(12.046)	Ethyl 2-mercaptopropionate		I
(12.047)	3-Mercaptobutan-2-one		I
(12.048)	2-Methylbutane-1-thiol		I

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

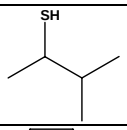
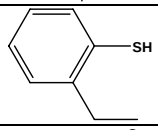
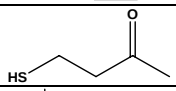
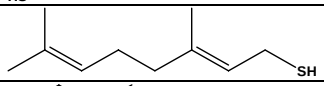
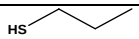
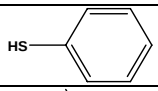
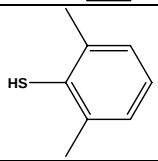
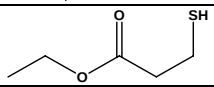
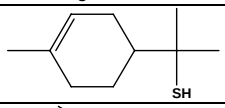
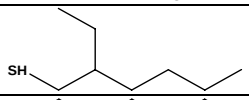
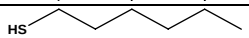
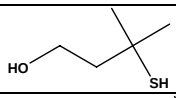
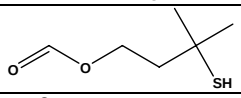
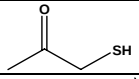
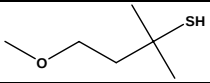
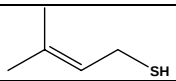
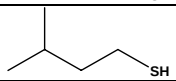
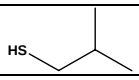
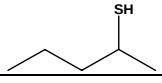
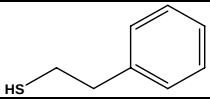
FL-no	EU Register name	Structural formula	Structural Class
(12.049)	3-Methylbutane-2-thiol		I
(12.054)	2-(Ethylthio)phenol		III
(12.055)	4-Mercaptobutan-2-one		I
(12.064)	Thiogeraniol		I
(12.071)	1-Propane-1-thiol		I
(12.080)	Thiophenol		II
(12.082)	2,6-(Dimethyl)thiophenol		II
(12.083)	Ethyl 3-mercaptopropionate		I
(12.085)	p-Menth-1-ene-8-thiol		II
(12.128)	2-Ethylhexane-1-thiol		I
(12.132)	Hexane-1-thiol		I
(12.137)	3-Mercapto-3-methylbutan-1-ol		I
(12.138)	3-Mercapto-3-methylbutyl formate		I
(12.143)	1-Mercaptopropan-2-one		I
(12.145)	4-Methoxy-2-methylbutane-2-thiol		I
(12.170)	3-Methylbut-2-ene-1-thiol		I
(12.171)	3-Methylbutane-1-thiol		I
(12.173)	2-Methylpropane-1-thiol		I
(12.192)	Pentane-2-thiol		I
(12.194)	2-Phenylethane-1-thiol		II

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

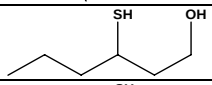
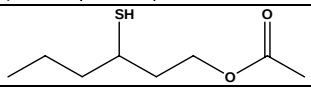
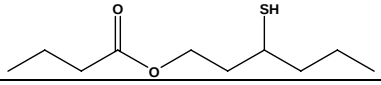
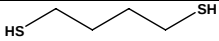
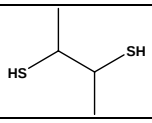
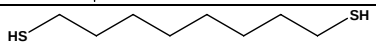
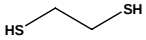
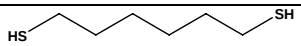
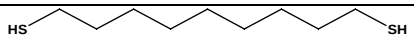
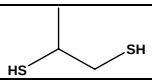
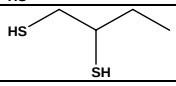
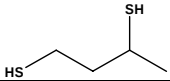
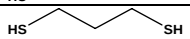
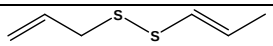
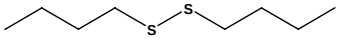
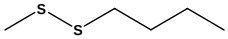
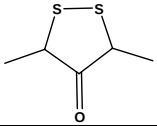
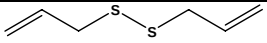
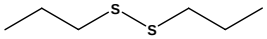
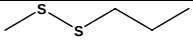
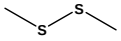
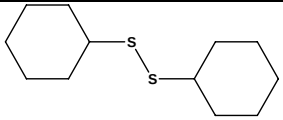
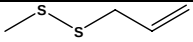
FL-no	EU Register name	Structural formula	Structural Class
(12.197)	Propane-2-thiol		I
(12.217)	3-Mercaptohexan-1-ol		I
(12.234)	3-Mercaptohexyl acetate		I
(12.235)	3-Mercaptohexyl butyrate		I
IV: DITHIOLS			
12.103	Butane-1,4-dithiol		I
(12.022)	Butane-2,3-dithiol		I
(12.034)	Octane-1,8-dithiol		I
(12.066)	Ethane-1,2-dithiol		I
(12.067)	Hexane-1,6-dithiol		I
(12.069)	Nonane-1,9-dithiol		I
(12.070)	Propane-1,2-dithiol		I
(12.072)	Butane-1,2-dithiol		I
(12.073)	Butane-1,3-dithiol		I
(12.076)	Propane-1,3-dithiol		I
V: ACYCLIC AND CYCLIC DISULPHIDES			
12.098	Allyl prop-1-enyl disulfide		II
12.111	Dibutyl disulfide		I
12.151	Methyl butyl disulfide		I
12.295	3,5-Dimethyl-1,2-dithiolane-4-one		II
(12.008)	Diallyl disulfide		II
(12.014)	Dipropyl disulfide		I
(12.019)	Methyl propyl disulfide		I
(12.026)	Dimethyl disulfide		I
(12.028)	Dicyclohexyl disulfide		II
(12.037)	Allyl methyl disulfide		II

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

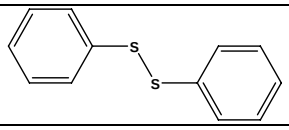
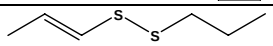
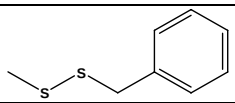
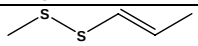
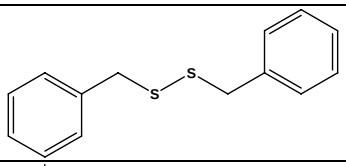
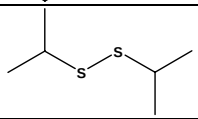
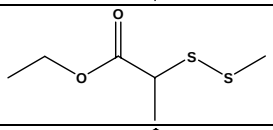
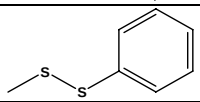
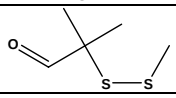
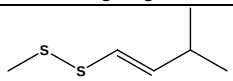
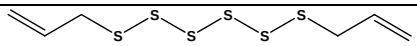
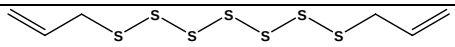
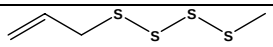
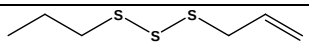
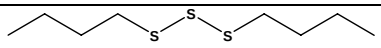
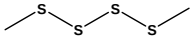
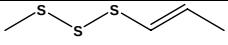
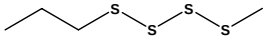
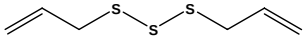
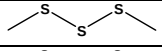
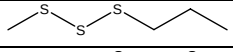
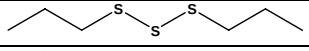
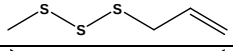
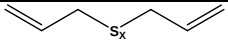
FL-no	EU Register name	Structural formula	Structural Class
(12.043)	Diphenyl disulfide		III
(12.044)	Prop-1-enyl propyl disulfide		I
(12.068)	Benzyl methyl disulfide		II
(12.075)	Methyl prop-1-enyl disulfide		I
(12.081)	Dibenzyl disulfide		II
(12.109)	Di-isopropyl disulfide		I
(12.121)	Ethyl 2-(methyldithio)propionate		I
(12.161)	Methyl phenyl disulfide		II
(12.168)	2-Methyl-2-(methyldithio)propanal		I
(12.218)	Methyl-3-methyl-1-butenyl disulphide		I
VI: ACYCLIC POLYSULPHIDES			
12.093	Diallyl hexasulfide		II
12.094	Diallyl heptasulfide		II
12.097	Allyl methyl tetrasulfide		II
12.100	Allyl propyl trisulfide		II
12.112	Dibutyl trisulfide		I
12.116	Dimethyl tetrasulfide		I
12.164	Methyl prop-1-enyl trisulfide		I
12.167	Methyl propyl tetrasulfide		I
(12.009)	Diallyl trisulfide		II
(12.013)	Dimethyl trisulfide		I
(12.020)	Methyl propyl trisulfide		I
(12.023)	Dipropyl trisulfide		I
(12.045)	Methyl allyl trisulfide		II
(12.074)	Diallyl polysulfides	 X=2,3,4 or 5	II

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

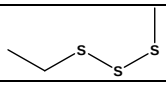
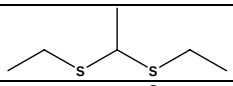
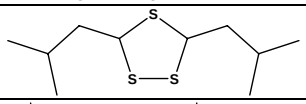
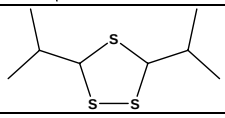
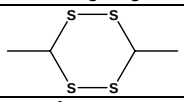
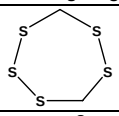
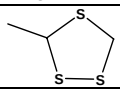
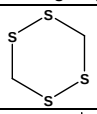
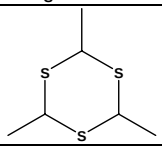
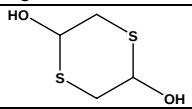
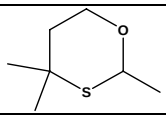
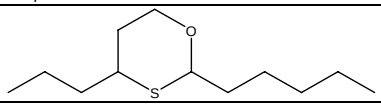
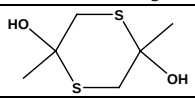
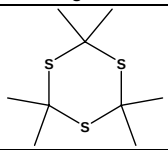
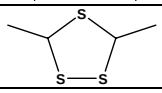
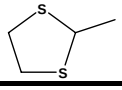
FL-no	EU Register name	Structural formula	Structural Class
(12.155)	Methyl ethyl trisulfide		I
VII: MONO-, DI- , TRI- AND POLYSULPHIDES WITH THIOACETAL STRUCTURE			
12.200	1,1-bis(Ethylthio)-ethane		I
15.047	3,5-Di-isobutyl-1,2,4-trithiolane		II
15.048	3,5-Di-isopropyl-1,2,4-trithiolane		II
15.056	3,6-Dimethyl-1,2,4,5-tetrathiane		II
15.081	Lenthionine		III
15.083	3-Methyl-1,2,4-trithiolane		II
15.103	1,2,4,5-Tetrathiane		II
15.110	2,4,6-Trimethyl-1,3,5-trithiane		II
15.111	1,2,4-Trithiolane		II
15.134	2,5-Dihydroxy-1,4-dithiane		III
16.057	2,4,4-Trimethyl-1,3-oxathiane		II
16.114	2-Pentyl-4-propyl-1,3-oxathiane		III
(15.006)	2,5-Dihydroxy-2,5-dimethyl-1,4-dithiane		I
(15.009)	Trithioacetone		II
(15.025)	3,5-Dimethyl-1,2,4-trithiolane		II
(15.034)	2-Methyl-1,3-dithiolane		II

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

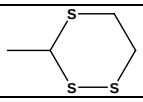
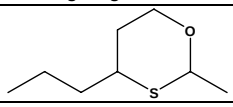
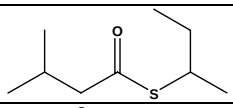
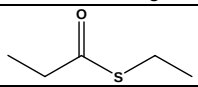
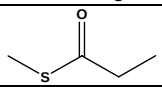
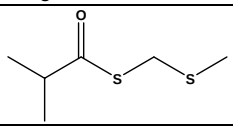
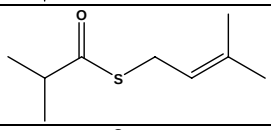
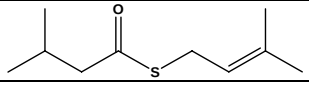
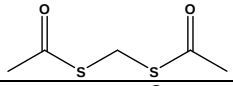
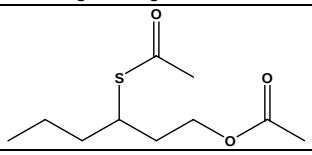
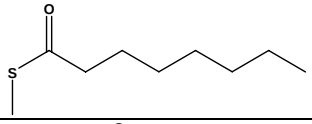
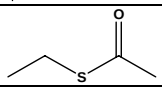
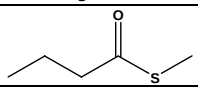
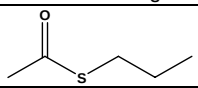
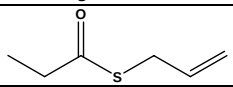
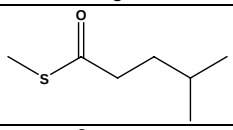
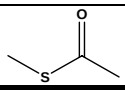
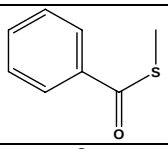
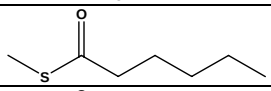
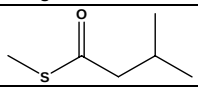
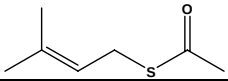
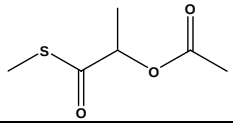
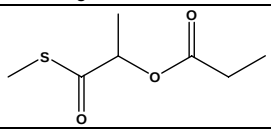
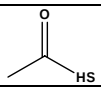
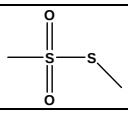
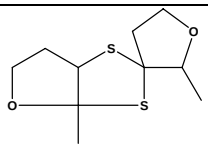
FL-no	EU Register name	Structural formula	Structural Class
(15.036)	3-Methyl-1,2,4-trithiane		II
(16.030)	2-Methyl-4-propyl-1,3-oxathiane		II
VIII: THIOESTERS			
12.106	S-2-Butyl 3-methylbutanethioate		I
12.125	Ethyl propanethioate		I
12.165	S-Methyl propanethioate		I
12.189	S-(Methylthiomethyl) 2-methylpropanethioate		I
12.196	S-Prenyl thioisobutyrate		I
12.221	S-Prenyl thioisopentanoate		I
12.271	Methanedithiol diacetate		I
12.278	3-Acetyl-mercaptohexyl acetate		I
12.282	(S)-Methyl octanethioate		I
(12.018)	S-Ethyl acetothioate		I
(12.032)	S-Methyl butanethioate		I
(12.059)	Propyl thioacetate		I
(12.101)	Allyl thiopropionate		I
(12.148)	S-Methyl 4-methylpentanethioate		I
(12.149)	S-Methyl acetothioate		I

Table 4.3.2 Subgroups - The supporting substances are listed in brackets

FL-no	EU Register name	Structural formula	Structural Class
(12.150)	S-Methyl benzothioate		II
(12.156)	S-Methyl hexanethioate		I
(12.157)	S-Methyl isopentanethioate		I
(12.195)	S-Prenyl thioacetate		I
(12.203)	Methylthio 2-(acetyloxy)propionate		I
(12.227)	Methylthio-2-(propionyloxy)propionate		I
IX: THIOIC ACID			
12.199	Ethanethioic acid		I
X: SULPHOXIDES/SULPHONES AND SULPHONATES			
12.159	Methyl methanethiosulfonate		III
(12.175)	Methylsulfinylmethane		III
XI: CYCLIC THIOKETAL WITH FUSED OXOLANE RINGS			
15.007	spiro(2,4-Dithia-1-methyl-8-oxa-bicyclo[3.3.0]octane-3,3'-(1'-oxa-2'-methyl)-cyclopentane) and spiro(Dithia-6-methyl-7-oxa-bicyclo[3.3.0]octane-3,3'-spiro(2,4-(1'-oxa-2-methyl)cyclopentane)		III

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ABBREVIATIONS

CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic acid
DTU-NFI	Danish Technical University – National Food Institute
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practise
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
ISS	Istituto Superiore di Sanita
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MMTS	Methyl methanethiosulfonate
MMS	Methanesulfonate
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NCE	Normochromatic erythrocyte
No	Number
NOAEL	No observed adverse effect level
NTP	National Toxicology Program

PCE	Polychromatic erythrocyte
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation